



New Methodologies Involving 1,2-Dioxines and Stabilised Phosphorus Ylides for Diastereoselective and Enantioselective Cyclopropanation

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Doctor of Philosophy

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Abstract

In the natural and non-natural product arena, enormous numbers of highly useful cyclopropyl containing compounds exist. The areas of insecticides, peptidomimetics and pharmaceuticals have experienced considerable interest from industry, thus, sanctioning the need for new and innovative methods for the preparation of enantiomerically-pure, highly substituted cyclopropanes. Two novel methods for the synthesis of di- and tri-substituted diastereomerically-pure and enantiomerically enriched cyclopropanes have been developed and will be discussed in intimate detail within this thesis.

Both new reactions centre on stabilised phosphorus ester ylides and their reaction with 3,6-disubstituted-1,2-dioxines, containing alkyl, aryl or hydrogen substitution. Proceeding through identical oxaphospholane intermediates it is the steric bulk of the ester moiety of the ylide, which is the determining element in the divergence of these two cyclopropane reactions. A full mechanistic description and scope of both reactions elucidated is outlined.

Additionally, improved methods for the synthesis of *cis* and *trans* γ -hydroxy enones from 1,2-dioxines and a study of their complex equilibria will be presented, as it was discovered early on that *cis* γ -hydroxy enones are the key intermediates in the reaction between ylide and 1,2-dioxine.

Catalytic formation of symmetrical *cis* γ -hydroxy enones from 1,2-dioxines utilising Co(SALEN)₂ type ligands has allowed for incorporation of enantiomeric excess into both cyclopropane pathways. Chiral catalysts allow formation of enantio-enriched *cis* γ -hydroxy enones, which upon reaction with ylides were found to yield enantio-enriched cyclopropanes.

Another intriguing result to arise from this research is that the cyclopropanation reactions remain unaffected by the presence of water making these very attractive reactions for industry. Deuterium oxide provided an excellent mechanistic probe enabling confirmation of both reaction manifolds. Given the enormous number of cyclopropyl

natural and non-natural products, application of tritium oxide to this reaction could lead to the synthesis of drug probes, especially in the growing area of peptidomimetics.

When synthesising cyclopropane natural products, it is often highly desirable to have a wide range of stereoisomers at hand. In this way, the effects that subtle changes in stereochemistry have on bioactivity can be elucidated. This thesis outlines preliminary procedures, exploiting the two cyclopropyl manifolds highlighted above, allowing for the preparation of closely related cyclopropyl di-acids.

Statement of Originality

This work contains no material which has been accepted for the award of any other degree or diploma in any other university or other tertiary institution and, to the best of my knowledge and belief, this thesis contains no material previously published or written by any other person, except where due reference has been made in the text.

I give consent to this copy of my thesis, when deposited in the University library, being available for loan or photocopying.

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Thomas Daniel Avery

20th November 2001
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Date

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Firstly this thesis could not have been written without the help and supervision provided by Dr. Dennis Taylor. Who, with his contagious enthusiasm for chemistry has inspired me throughout my Ph.D. and will continue to do so in the future.

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Abbreviations

AIBN	2,2'-azobisisobutyronitrile
Anal. Calc.	analysis calculated
Ar	aromatic
Bn	benzyl
Bu	butyl
Bu ^t	<i>tert</i> -butyl
CLS	chiral lanthanide shift
Co(SALEN) ₂	<i>N,N'</i> -bis(salicylidene)-ethylenediaminocobalt(II)
CoTPP	5,10,15,20-Tetraphenyl-21 <i>H</i> ,23 <i>H</i> -porphin cobalt (II)
d	day(s)
Δ	heat
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
de	diastereomeric excess
DMSO	dimethylsulphoxide
ee	enantiomeric excess
equiv.	equivalent(s)
Et	ethyl
EW	electron withdrawing group
GC	gas chromatography
gCOSY	gradient correlated spectroscopy
gHMBC	gradient heteronuclear multiple bond connectivity
gHMQC	gradient heteronuclear multiple quantum coherence
gHSQC	gradient heteronuclear single quantum coherence
h	hour(s)
HPLC	high-performance liquid chromatography
<i>hν</i>	irradiation
IR	infra red
L	ligand
LG	leaving group
M	moles per litre

<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
<i>m/z</i>	mass to charge ratio
Me	methyl
MHz	megahertz
MIRC	Michael initiated ring closure
mol	mole(s)
NMR	nuclear magnetic resonance
<i>p</i> -TSA	<i>para</i> -toluene sulphonic acid
Ph	phenyl
ppm	parts per million
Pr ^{<i>i</i>}	isopropyl
rds	rate determining step
R _f	retention factor
ROESY	rotating frame overhauser enhancement spectroscopy
rt	room temperature
S _N 2	bimolecular nucleophilic substitution
TBDPS	<i>tert</i> -butyldiphenylsilyl
TEA	triethylamine
TEMPO	(2,2,6,6)-tetramethyl-1-piperidinyloxy, free radical
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl, tetramethylsilane
TPP	triphenyl phosphine
TPPO	triphenyl phosphine oxide
UV	ultra violet

If you never did, you should. These things are fun, and fun is good.

- Dr. Seuss

Chapter 1: General Introduction

Cyclopropyl Natural Products

The cyclopropyl motif is represented in a wide variety of natural products, transient metabolites and intermediates within the biosynthetic pathways of all living organisms.¹⁻³ These naturally occurring compounds provide attractive synthetic targets, as they have many desirable biological and chemical properties. Modification of these compounds has also led to the creation of compounds with enhanced and novel functions. For example, the insecticidal properties of pyrethroids (**1**),⁴ have received considerable attention in the creation of commercially available products due to their specific targeting of insects and bio-degradable nature. Also drugs such as Efavirenz (**2**) and Abacavir (**3**), which both act as reverse transcriptase inhibitors of high efficacy are currently employed in the treatment of HIV type 1.^{5,6}

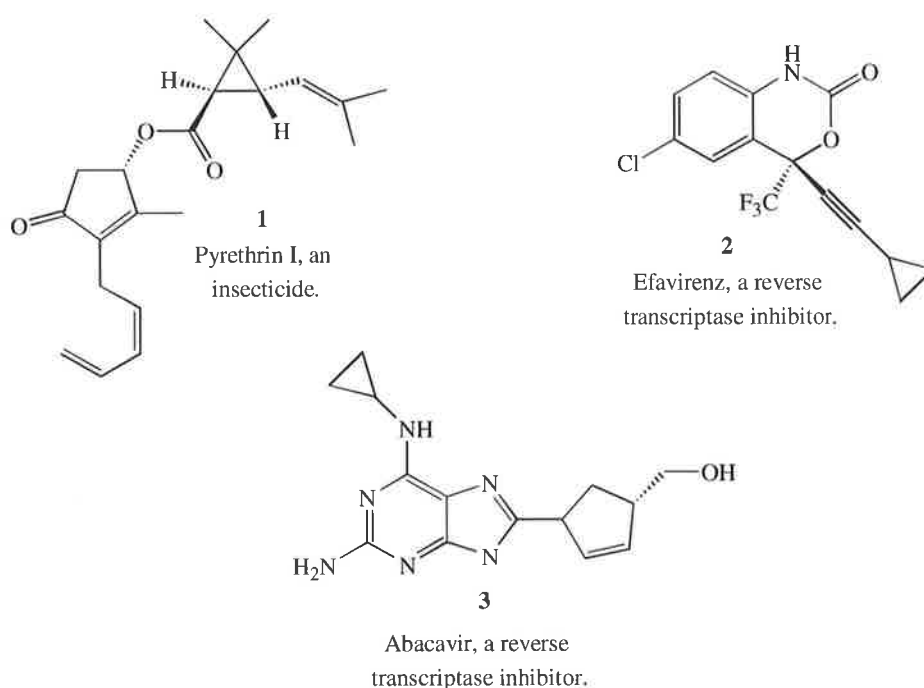


Figure 1. Cyclopropane containing biologically active compounds.

The compounds mentioned above are but three of the countless cyclopropyl containing molecules that have found application in the modern world. Many other biologically active cyclopropyl products include anti-mitotic agents,⁷ collagenase inhibitors,⁸ antiviral agents,⁹ DNA polymerase inhibitors,¹⁰ antidepressants,¹¹ protease inhibitors,¹² immunosuppressants¹³ and anti-inflammatory agents,¹⁴ highlighting the ubiquitous nature of the cyclopropyl moiety.

Two important and topical areas of research involving the cyclopropyl group are those of antibiotics and peptidomimetics. In recent years the increase in antibiotic resistance of bacteria, such as the deadly *Staphylococcus aureus*, has prompted the search for new and more effective antibiotics. Several antibiotics that contain cyclopropyl moieties include ambruticins (orally active antifungal/antibiotics) (**4**)^{15,16} and marasmic acid (**5**), a potent antibiotic against *Escherichia coli* and *Staphylococcus aureus*.³

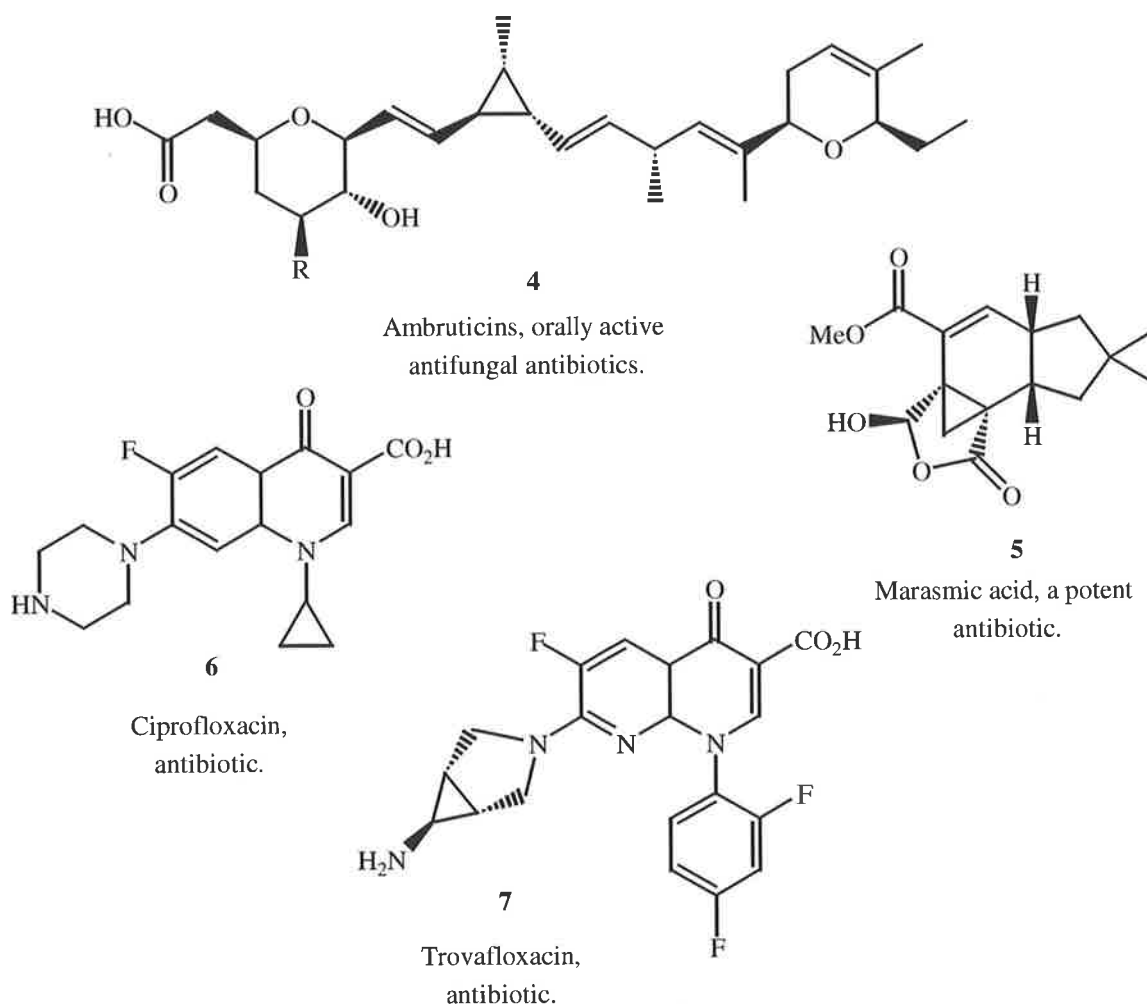


Figure 2. Cyclopropyl containing antibiotics.

More recently a major class of antibiotics, the fluoroquinolones, have been investigated as they show considerable potential in the treatment of *Mycobacterium tuberculosis* and *Sterptococcus pneumoniae* infections.² This large class of antibiotics is heavily reliant on the cyclopropyl moiety for function and is represented by Ciprofloxacin (**6**) and Trovafloxacin (**7**), Figure 2.

As mentioned above the cyclopropyl motif also plays a significant role in the field of peptidomimetics.^{17,18} Peptidomimetics are biologically active molecules and are designed to mimic the characteristics of bioactive proteins. Proteins, although having unsurpassed ability in carrying out the chemical processes for which they were evolved, generally make poor pharmaceuticals.¹⁹ The primary reason for this is that proteins have virtually non-existent oral bioavailability, due to proteolysis, and their high manufacturing cost. Circumventing these obstacles, peptidomimetics are more robust, smaller and more cost effective mimics of desired proteins based upon the original proteins functionality. The cyclopropane moiety can be made use of in peptidomimetics, usually as cyclopropyl amino acids, where it is the sterically hindered framework of the cyclopropyl ring, which imparts rigidity and stability to the peptide analogues. Rigidity is important for maintaining the shape of these peptide mimics, as the large protein scaffolding that fixes the tertiary structure of a protein is absent.

Several cyclopropyl amino acid derivatives such as (-)-*Allo*-norcoronamic acid (**8**), (2*S*, 1'*S*, 2'*S*)-2-(carboxycyclopropyl)glycine (L-CCG-I) (**9**) and peptide mimic (**10**), Figure 3, have been used in peptidomimetics.^{18,20,21} The L-glutamate analogue (**9**) has also been found to be a selective agonist for group II metabotropic glutamate receptors.²¹ Furthermore, modification of this compound at the currently unsubstituted position on the cyclopropyl ring could potentially generate new anti-epileptic drugs.²² Peptide mimic (**10**) has been found to be an HIV-1 protease inhibitor.¹⁸

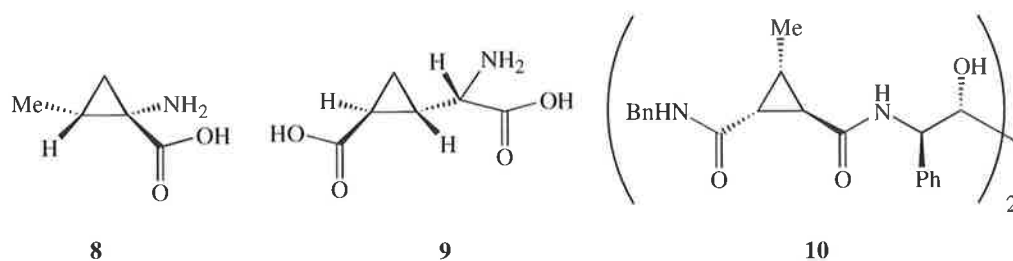


Figure 3. Cyclopropyl amino acid derivatives.

Antibiotics and peptidomimetics are only two of the myriad of uses for compounds containing the cyclopropyl moiety. Therefore, given the broad scope of important or potentially important cyclopropyl containing compounds further discussion will be limited to cyclopropyl containing targets that could potentially be prepared utilising the new cyclopropyl syntheses outlined within this thesis.

Aragusterols A, B, C and D in Figure 4 were isolated from the Okinawan marine sponge, genus *Xestosphgia*, and exhibit a rare cyclopropane motif in the side chain of the D ring.²³

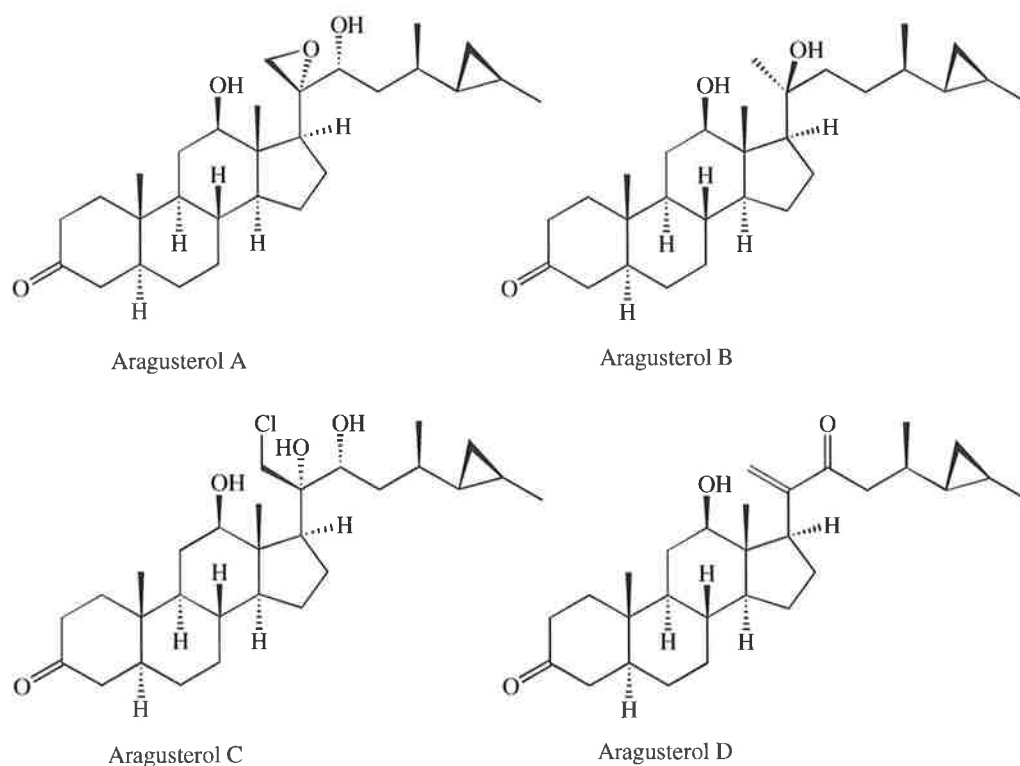


Figure 4. Aragusterols.

Steroids A and C have demonstrated very strong *in vivo* antitumor activity and have yet to be synthesised, making them attractive targets.

Mycolic acids are high molecular weight α -alkyl, β -hydroxy cyclopropyl containing fatty acids.²⁴⁻²⁶ The cell wall of the human tuberculosis bacilli (*Mycobacterium tuberculosis*) includes these fatty acids and it is believed that these protect the bacilli against detrimental environmental conditions and chemotherapeutics.

Tuberculosis kills more than three million people a year worldwide and is the leading cause of death in immuno-compromised AIDS patients.^{27,28} These deaths are generally in Asia and Africa, however, there is an increasing number of cases arising in Western society. Antimycobacterial agents such as isoniazid, ethambutol, rifampin and pyrazinamide are currently used in fighting the disease. Many of these drugs also contain cyclopropyl moieties.^{27,28}

The *Taylor* group has been pursuing the synthesis of mycolic acid (**11**) represented in Figure 5, with aim of the elucidating the absolute stereochemistry of the two *cis* cyclopropyl groups found in the fatty acid chain. Knowledge of the absolute stereochemistry of the cyclopropyl groups could provide a means to develop improved drugs to combat the bacterium.

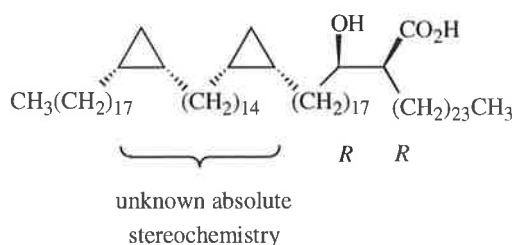


Figure 5. Mycolic acid target (**11**).

PHYLPA (phylarum lysophosphatidic acid) (**12**) is a specific inhibitor of DNA polymerase α in eukariotic cells, which is the primary enzyme sequestered and put to use by various viruses in order for them to replicate.¹⁰ Therefore, PHYLPA and its derivatives are attractive targets, which could lead to possible treatments for viral

infections through the prevention of replication of viral DNA. A partial synthesis of PHYLPA has been performed within the *Taylor* group,²⁹ with the aim of improving the synthesis.¹⁰

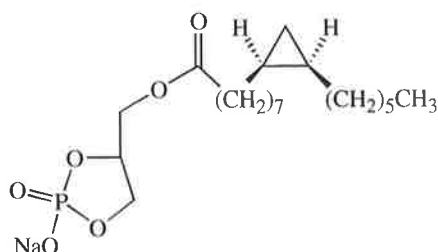


Figure 6. PHYLPA (**12**).

Grenadadiene (**13**), debromogrenadadiene (**14**) and grenadamide (**15**) are all cyclopropyl fatty acid natural products isolated from a marine cyanobacteria *Lyngbya majuscula*.³⁰ These three compounds are yet to be synthesised and their absolute stereochemistry assigned. The *Taylor* group intends to synthesise these compounds and their derivatives in order to test the compounds for possible anticancer, antiviral and antibiotic properties.³¹

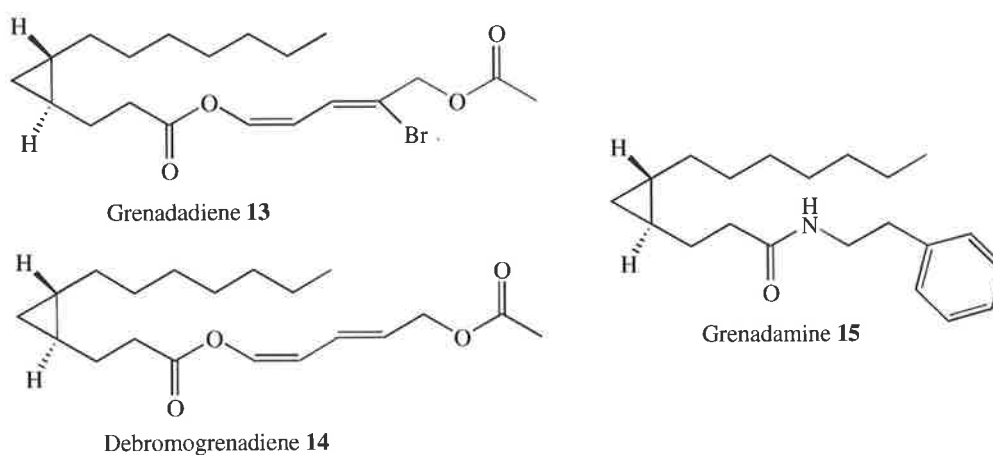


Figure 7. Cyclopropyl containing metabolites of the marine cyanobacterium *Lyngbya majuscula*.

Synthesis of Optically Active Cyclopropanes

For many of the bioactive compounds discussed above, it is the cyclopropyl group that plays an integral role in their bioactivity. Therefore, due to the stringent stereochemical requirements of biological receptors, it is critical that enantiomers of these cyclopropyl-containing chemicals be obtained. The abundant substitution about the cyclopropane ring in many natural products and the requirement of high enantiomeric excess creates considerable synthetic challenges.

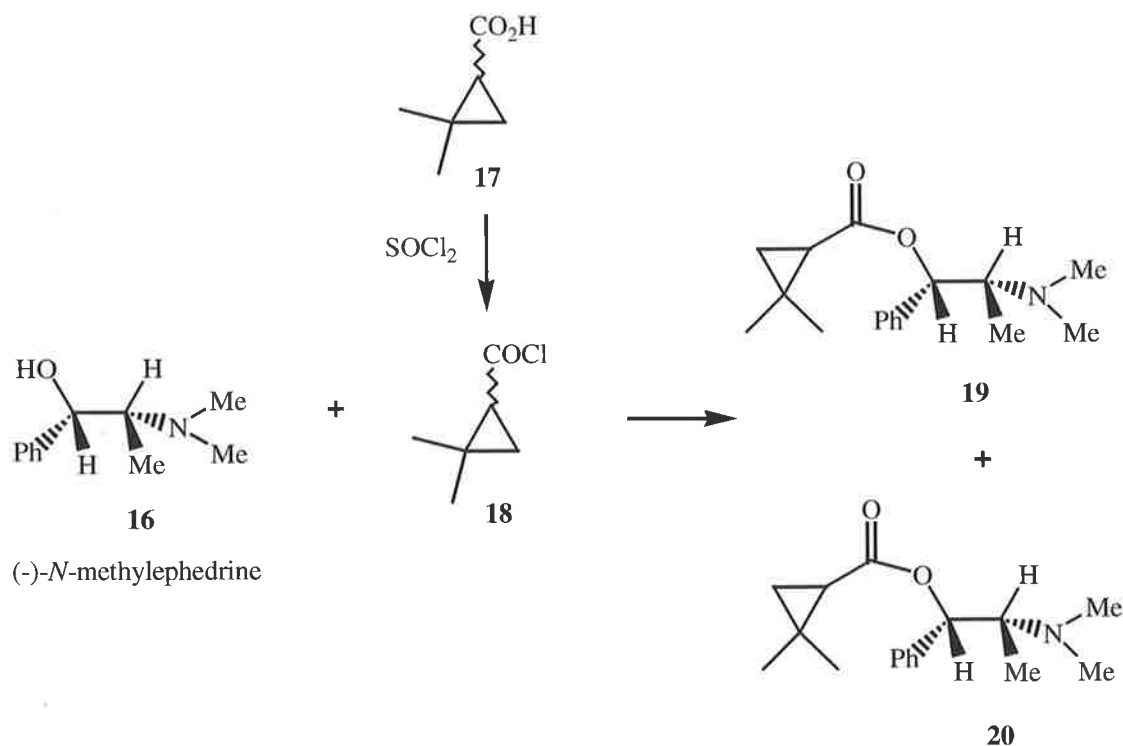
Four strategies of great importance in the area of enantiomerically-pure cyclopropane construction are (i) enantiomeric resolution of either cyclopropanes or their precursors; (ii) transition metal catalysed carbene transfer to olefins; (iii) nitrogen extrusion from Δ^1 -pyrazolines and (iv), Michael initiated ring closure (MIRC) reactions.

Enantiomeric resolution and separation of cyclopropanes or their precursors

The enantiomeric resolution and separation of cyclopropanes and their precursors can be performed using traditional chemical techniques or through microbial/enzymatic techniques.³² Resolution, through, traditional methods include the use of chiral resolving agents, typically optically active alcohols, amines, acids and aldehydes, being attached to either cyclopropanes or their precursors, thus, generating diastereomers. Resolution of the diastereomers can then be performed using HPLC, column chromatography or through recrystallisation. Formation of enantiomerically-pure precursors to cyclopropanes, can also be achieved though utilising other chiral syntheses.

One example of using traditional methods to separate cyclopropane enantiomers, which is pertinent for the discussions within Chapter 6, involves the use of (-)-*N*-methylephedrine (**16**) to resolve cyclopropane carboxylic acid (**17**), Scheme 1.^{32,33}

Scheme 1



resultant diastereomers can be resolved by recrystallisation of their hydrochloride salts or chromatography.

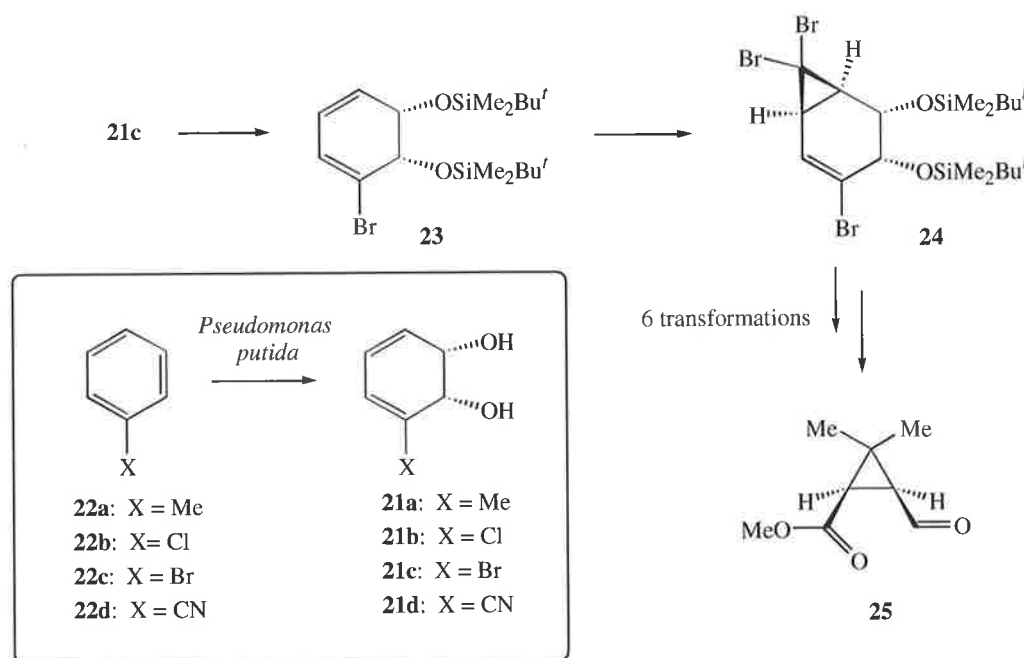
Cyclopropyl acid (**17**) was firstly converted into its corresponding acid chloride (**18**) in the presence of thionyl chloride. Treatment of the acid chloride (**18**) with (-)-*N*-methylephedrine (**16**) resulted in the formation of cyclopropyl ester diastereomers (**19**) and (**20**). Precipitation of the hydrochloride salt of the diastereomeric mixture from HCl, resulted in the precipitated salt containing a 97.5 : 2.5 ratio of isomers (**19**) : (**20**) and the supernatant containing a ratio of 18.6 : 81.4 respectively. Alternatively, the ester diastereomers were separated and isolated through the use of chromatography.

Microbial/enzymatic enantiomeric resolution and separation of cyclopropanes or their precursors are represented by very specific examples.³² One example utilising microbial techniques to generate enantiomerically-enriched cyclopropanes involves *cis*-1,2-dihydrocatechols of type (**21**), Scheme 2.³⁴ *cis*-1,2-Dihydrocatechols have not only been utilised in the construction of enantiomerically-enriched cyclopropanes, but also for the asymmetric synthesis of a wide range of other natural products.³⁵⁻³⁷

cis-1,2-Dihydrocatechols are synthesised in high ee (>98%) via *Pseudomonas putida* mediated oxidation of mono-substituted benzene adducts (**22**).³⁵

In a first generation partial synthesis of (1*R*)-*cis*-pyrethroids, Banwell *et al.* initially protected *cis*-1,2-Dihydrocatechol (**21c**) as the di-(*tert*-butyldimethylsilyl) ether (**23**), which was then cyclopropanated using dibromocarbene to generate cyclopropyl derivative (**24**), Scheme 2.³⁴ Once the cyclopropane ring was formed, the target synthon (**25**) was obtained in high ee through six subsequent transformations.

Scheme 2



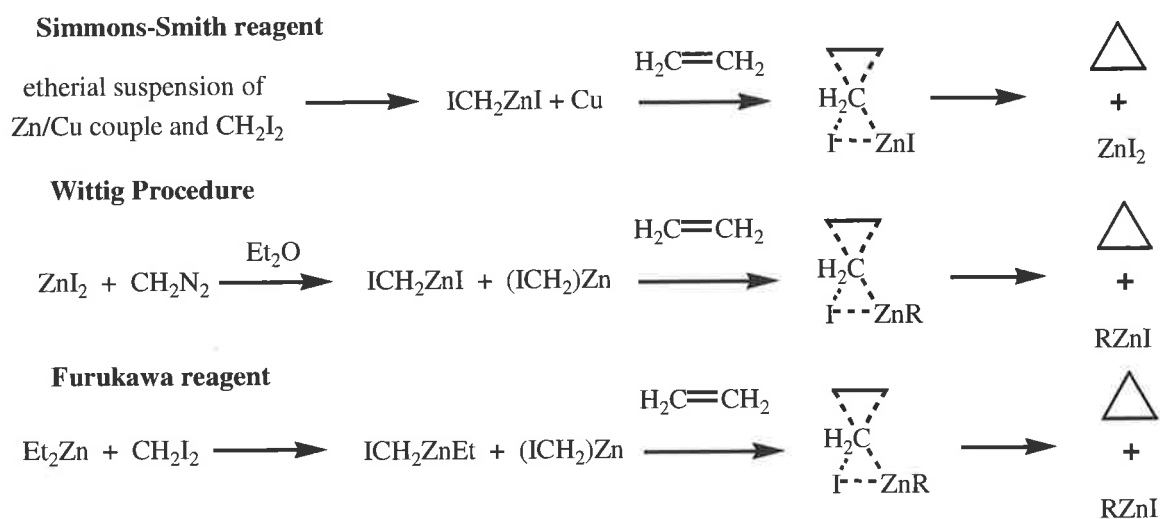
Transition metal catalysed carbene transfers to olefins

Asymmetric transition metal catalysed carbene transfer reactions can be performed via two major methods (i) Simmons-Smith carbene transfer,^{32,38-40} or (ii) transition metal carbene transfer from diazo precursors.^{32,40,41}

Simmons-Smith type reactions rely upon the generation of a carbenoid species, these can be prepared via three major methods, (i) Zn-Cu, Zn-Ag, Sm-Hg couple and dihaloalkane,

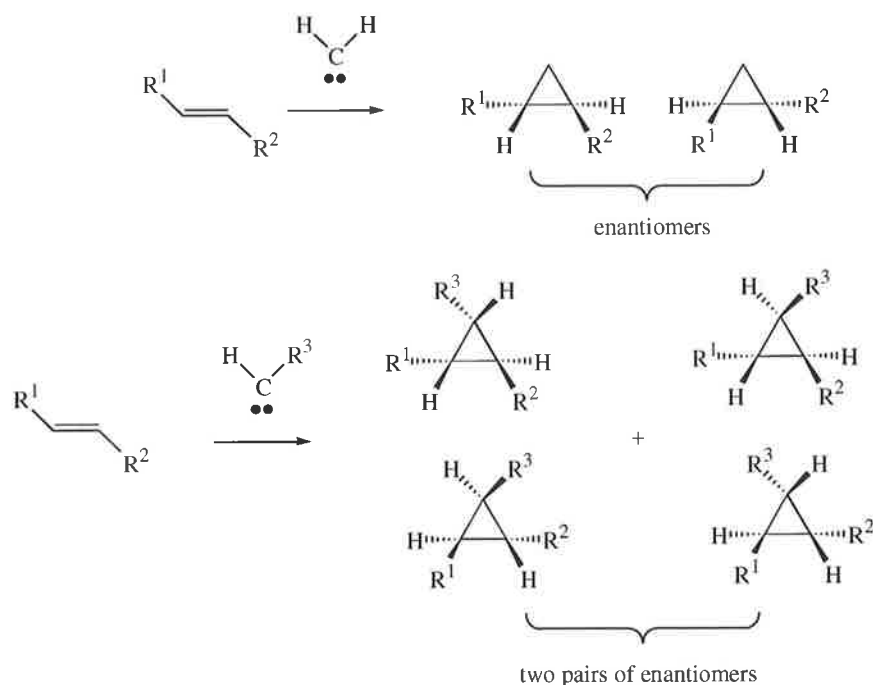
an example of which is the original Simmons-Smith reaction,⁴² or (ii) the action of Zn(II) salt and diazoalkane, developed by Wittig *et al.*,⁴³ or (iii) the reaction of diethylzinc and dihaloalkane, also referred to as the Furukawa procedure.⁴⁴ Once generated the carbenoid species then delivers methylene or a higher analogue across an olefin to form the cyclopropyl moiety, Scheme 3.

Scheme 3



Asymmetric syntheses utilising Simmons-Smith type reagents have, for the main part, been concerned with the addition of methylene to alkenes as they generate only one enantiomeric pair, Scheme 4. The use of higher carbene analogues for the asymmetric synthesis of 1,2,3-trisubstituted cyclopropanes has also been achieved, however, with limited control of the diastereomeric ratio and only average ee.^{45,46} This is due to the generation of another enantiomeric pair and the difficulties encountered in favouring the formation of just one enantiomer, Scheme 4.

Scheme 4



The most significant advance in the area of asymmetric Simmons-Smith reactions came with the observation that the presence of a proximal oxygen atom considerably enhances the rate and stereoselectivity of the reaction.⁴⁵ This basic premise has been exploited in virtually all asymmetric Simmons-Smith reactions.

The introduction of chirality into the Simmons-Smith transformation can be achieved in one of two ways; (i) via the use of reactant-bound chiral auxiliaries or (ii) the presence of a chiral reagent in a stoichiometric or catalytic amount; both techniques can be used simultaneously.

The first method relies on a reagent bound chiral auxiliary containing a proximal oxygen functional group; these groups include free hydroxyl groups, esters, ethers, acetals, ketals and vinyl boronates.³⁸ One of the most successful and widely employed methods involves the use of tartaric acid derivatives, shown in Figure 8.

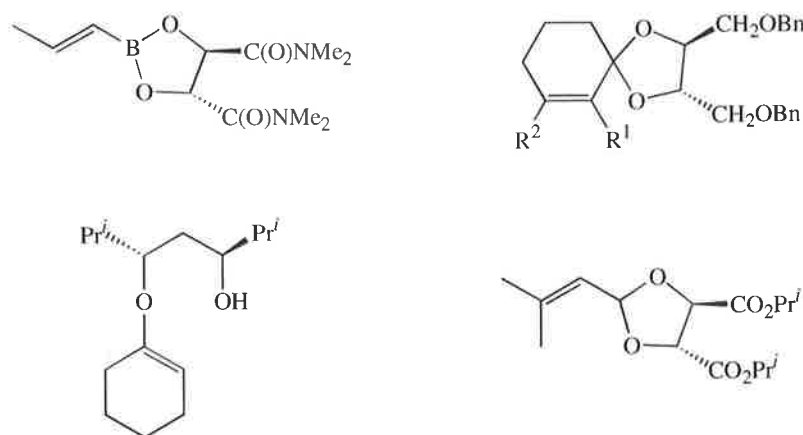
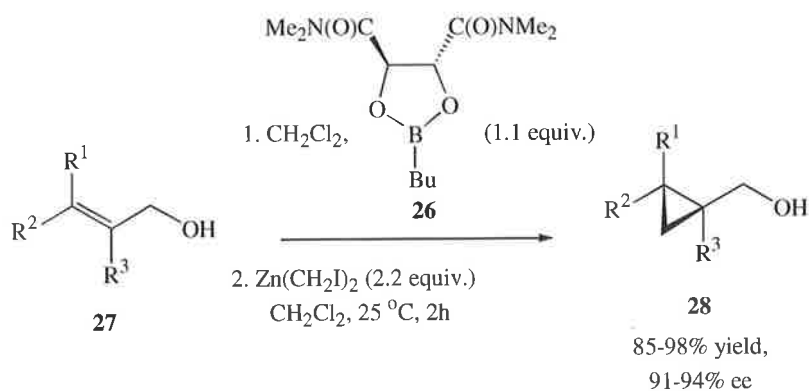


Figure 8. Various tartrate auxiliaries demonstrating the variety of proximal oxygen functional groups used in cyclopropanation.

Generation of cyclopropanes using the chiral auxiliaries depicted in Figure 8 results in the formation of two cyclopropyl diastereomers, arising from attack at either face of the alkene. The isomers can be resolved at this stage by chromatography or recrystallisation; or if the diastereomeric ratio is high enough, removal of the chiral auxiliary will yield highly enantiomerically-enriched cyclopropane.

The second method for generating enantiomerically-pure cyclopropanes, from Simmons-Smith reactions, typically involves the use of chiral compounds designed to complex the halomethylzinc reagent and alkene simultaneously. This can either be performed in a stoichiometric or catalytic manner.^{38,40,47} One of the best examples is the employment of a stoichiometric amount of dioxaborolane (**26**) with allylic achiral alcohols of type (**27**) which are allowed to react with halomethylzinc reagent, pre-formed by the reaction of diethylzinc and diiodomethane (Furukawa procedure), Scheme 5.^{48,49} This reaction is high yielding and generates cyclopropanes (**27**) of high ee. Furthermore, the chiral reagent can be recycled and the cyclopropane purified by simple extraction of the resultant reaction mixture.

Scheme 5



These factors make this reaction extremely attractive for natural product synthesis and it has recently been employed in the elegant synthesis of FR-900848 (a potent antifungal agent) and U-106305 (a cholesterol ester transferase protein inhibitor).⁵⁰⁻⁵⁴

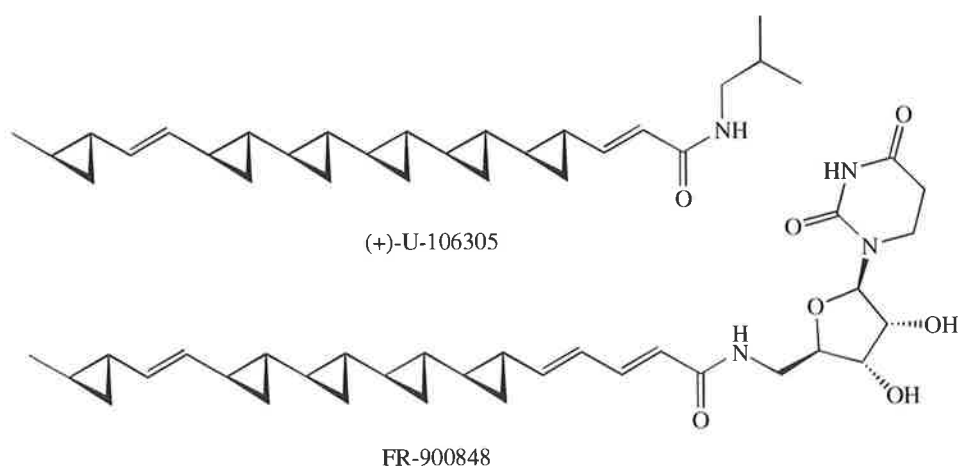


Figure 9. Polycyclopropyl natural products.

Two methodologies have emerged in recent times to effect the catalytic chiral catalysis of cyclopropane formation from allylic alcohols in much the same way as demonstrated in Scheme 5. The catalysts (**29**) and (**30**) utilised in these reactions enable ee within the range 60-89% to be incorporated into the cyclopropyl products.^{46,55}

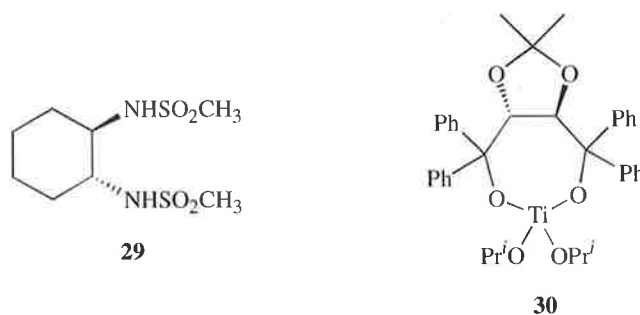
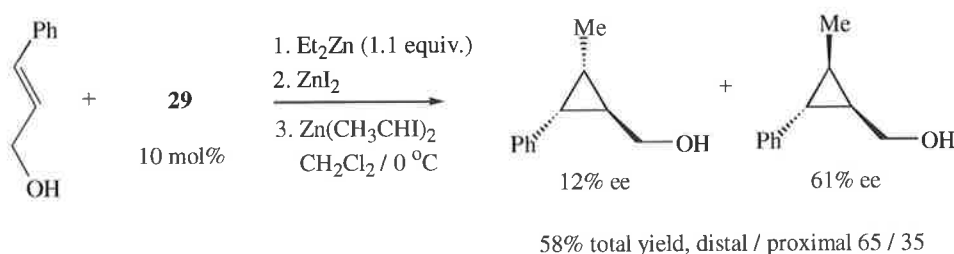


Figure 10. Chiral catalysts for the cyclopropanation of allylic alcohols.

At the present time efficient asymmetric syntheses are restricted to generation of 1,2-substituted cyclopropanes, limiting the Simmons-Smith methodology. Furukawa *et al.* demonstrated early on, that stereoselective ethylidenation was possible by exploiting steric hindrance, and chiral hydroxyl groups in very specific examples, to generate 1,2,3-substituted cyclopropanes.⁴⁵ Recently, Denmark *et al.* demonstrated the best, to date, asymmetric synthesis of 1,2,3-substituted cyclopropanes utilising (29) as a catalyst, Scheme 6.⁴⁶

Scheme 6

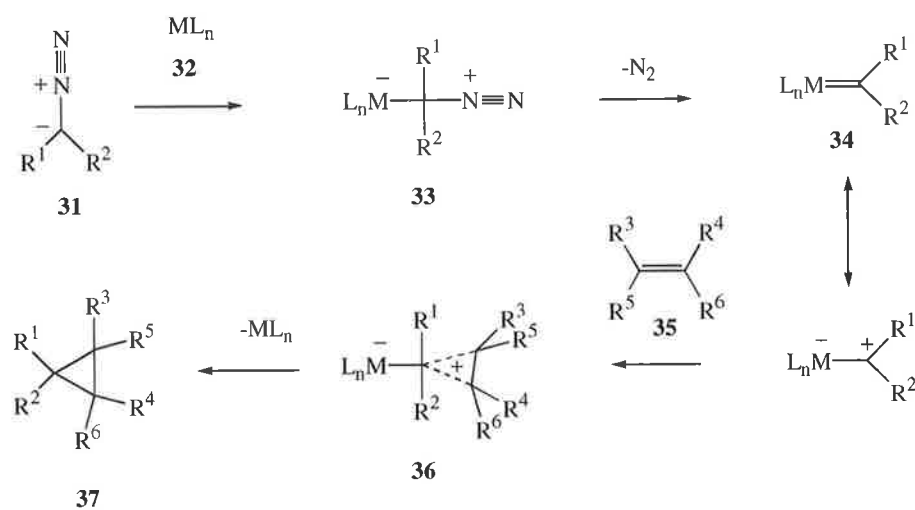


This reaction is only mildly diastereo- and enantio-selective but lays the foundation for further developments in the area of catalysis as well as the formation of enantiomerically-pure 1,2,3-trisubstituted cyclopropanes from Simmons-Smith type reactions.

The second widely employed method for the asymmetric transfer of carbenes to olefins, exploits the use of transition metal catalysts and diazo precursors.^{32,40,41} A typical reaction, Scheme 7, shows the complexation of a diazo compound (31) to the metal centre

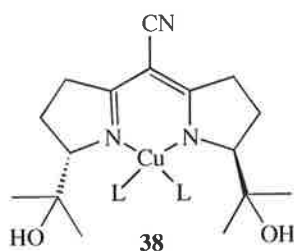
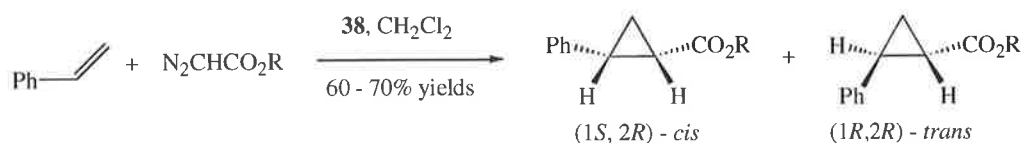
(M) of chiral ligand (**32**). Extrusion of nitrogen from complex (**33**) leads to the formation of a carbenoid species (**34**). Complexation of the olefin (**35**) generates the transitional species (**36**). It is the orientation of formation of (**36**) that dictates the final diastereomeric and enantiomeric ratios of the cyclopropyl products (**37**). Creation of cyclopropane (**37**) and liberation of the metal complex restarts the catalytic cycle.

Scheme 7



Transition metals Rh, Cu, Pt, Co and Ru are suitable for this type of reaction along with a host of complex chiral ligands.^{32,40,41} Diazoacetate derivatives are the diazo compounds of choice for these reactions due to the functionality imparted to the cyclopropyl product. Bulky chiral diazoacetate derivatives such as (+/-) menthyl are also commonly used to increase the diastereo- and enantio-selectivity of the reaction, Scheme 8. Many methods now exist for the synthesis of enantiomerically-pure cyclopropanes via this route.^{32,40,41,56-58} It is, however, poor diastereoselection and low generality of each catalyst to variations in substrate that plagues these procedures. In the case of the Pfaltz procedure depicted within Scheme 8, the ees are high for both *cis* and *trans* isomers, however, there is only moderate diastereoselectivity. There is also poor application of this procedure to other olefinic substrates such as disubstituted or trisubstituted alkenes.^{40,41}

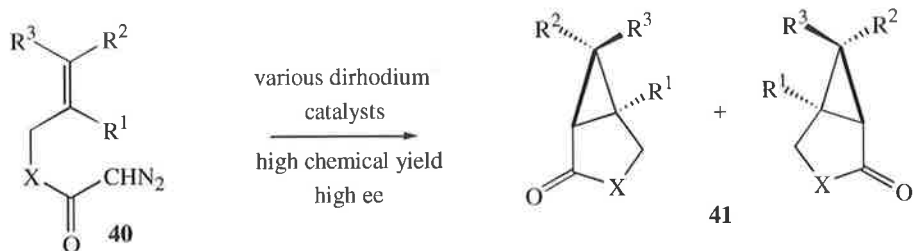
Scheme 8



R =	% ee (cis)	trans : cis	% ee (trans)
Et	80	73 : 27	92
Bu ^t	92	81 : 19	93
<i>d</i> -menthyl	95	82 : 18	97
<i>l</i> -menthyl	90	85 : 15	91

Advances in the generality and diastereoselectivity of these types of reactions have been made in the area of intramolecular reactions mediated by dirhodium catalysts (**39**) Scheme 9.^{41,59,60}

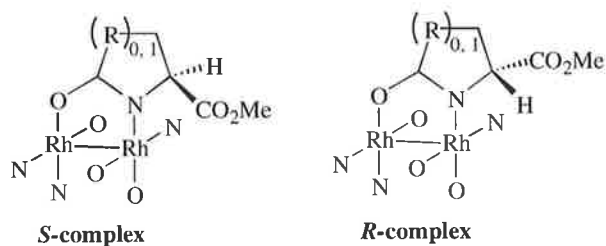
Scheme 9



both enantiomers available from *R* or *S* catalyst.

X = O, N, NMe, NBu^t

larger lactone or lactam ring systems of varying substitution are also possible, however, in generally lower yield and ee



39

R = CH₂, O, NC(O)alkyl each dirhodium(II) core is bound to 4 ligands.

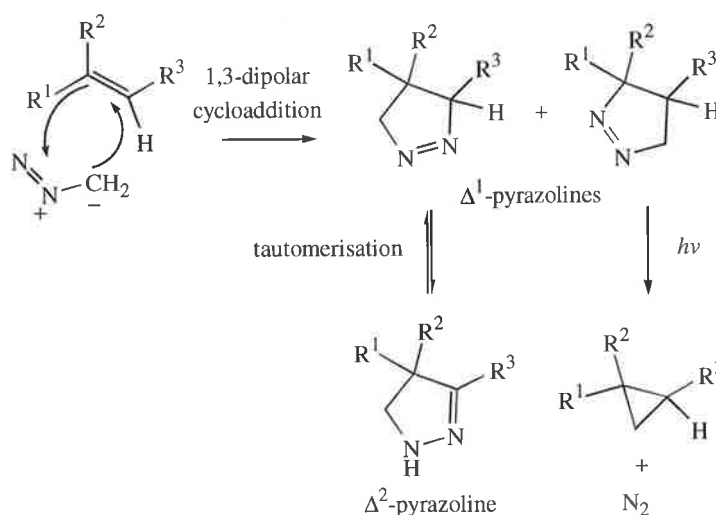
These catalysts have been used in intermolecular reactions and exhibit high enantiomeric and moderate diastereomeric excess, however, lower than that of copper catalysts such as (38).^{61,62} Intramolecular reactions require only very slight modifications to these dirhodium catalysts (39) in order to provide extremely high ees when allowed to react with a wide range of substrates (40), of varying substitution. It is also possible to obtain the opposite cyclopropyl enantiomer by utilising the opposite enantiomer of the catalyst, Scheme 9. The resulting highly substituted cyclopropanes (41) have been used with great success in numerous natural product syntheses.⁴¹

Other examples of transition metal carbenoids for asymmetrical cyclopropanation are present in the literature and involve metals such as Fe, Cr, Pd and Ni.³² The methods of carbenoid formation are quite specific for each example, however, they all follow the basic premise that, chiral ligands about the coordinating metal, direct the asymmetric cyclopropanation of olefins.

Nitrogen extrusion from Δ^1 -pyrazolines

Δ^1 -Pyrazolines are readily formed by the 1,3-dipolar cycloaddition of diazo-derivatives to olefins, Scheme 10. Photolytic extrusion of nitrogen and cyclisation to afford cyclopropane proceeds with retention of configuration via a di-radical mechanism.⁶³

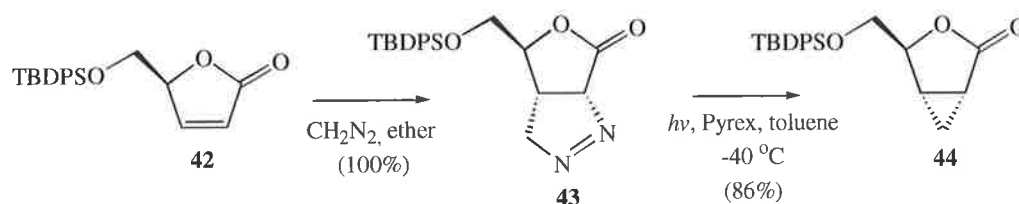
Scheme 10



Chirality is introduced firstly via the use of reagent bound chiral auxiliaries to direct the diastereoselective π -facial 1,3-dipolar cycloaddition of diazomethane derivatives to olefins.⁶⁴⁻⁶⁹ One limitation of this procedure worth discussing is the ability of some Δ^1 -pyrazolines to undergo tautomerisation to give the corresponding Δ^2 -pyrazoline, Scheme 10, which presents two major problems. Firstly, it enables racemisation of one of the chiral centers contained within the Δ^1 -pyrazoline and secondly, Δ^2 -pyrazolines are poor nitrogen extruders. Therefore, design of the olefinic substrate must take these two factors into account. A common method for circumventing this problem is to generate Δ^1 -pyrazolines, which do not readily undergo tautomerisation. This can be achieved by designing compounds where protons of limited acidity are located in the positions α to the N=N linkage. One other factor that must be considered is the photostability of the olefinic substrate.

One such effective method for the asymmetric synthesis of cyclopropanes is the use of chiral furanones such as (**42**) as the olefinic substrate.⁶⁵ These substrates are readily obtained from enantiomerically-pure commercially available glyceraldehyde. As seen in Scheme 11, addition of diazomethane to this type of enantiomerically-pure precursor affords a quantitative yield of Δ^1 -pyrazoline (**43**) in >99% de. Δ^1 -pyrazoline (**43**) was subsequently converted into cyclopropane (**44**) via photolysis in good yield. Cyclopropane (**44**) was then utilised for the synthesis of enantiomeric precursors to cyclopropyl aminoacids.⁶⁵

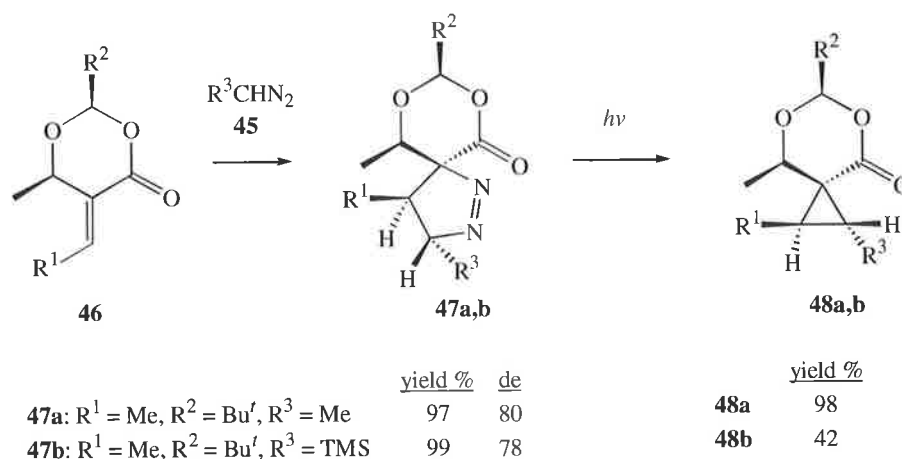
Scheme 11



Not only has this technique been used for the synthesis of chiral 1,2-disubstituted cyclopropanes, it has also been utilised in the synthesis of 1,2,3-trisubstituted

cyclopropanes. This has been achieved through the use of higher diazomethane analogues (**45**), Scheme 12.⁶⁴

Scheme 12

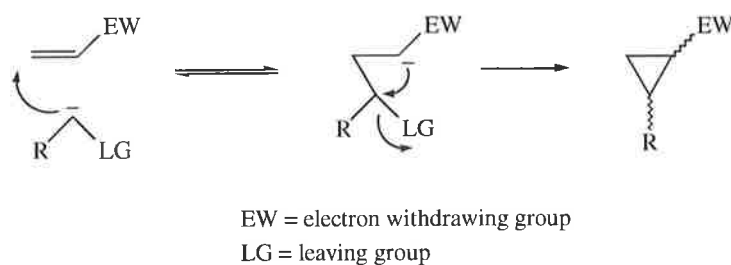


Although the diastereomeric excess is not very high, the diastereomers of the Δ^1 -pyrazolines (**47a,b**) and those of the cyclopropanes (**48a,b**) proved easily separable by column chromatography or recrystallisation. This gave rise to de >98% which in turn resulted in the high ee of the deprotected cyclopropane. It is worth noting that this procedure is excellent for the synthesis of chiral 1,2-disubstituted cyclopropanes where R³ = H, Scheme 12.

Michael initiated ring closure (MIRC) reactions

The last mode of cyclopropanation to be discussed is the MIRC reaction, which is the mode via which the two cyclopropanation reactions described within this thesis proceed. MIRC is the broad term given to a class of ring forming reaction which involves the nucleophilic conjugate addition of a substrate to an α,β -unsaturated electron withdrawing group, Scheme 13. Subsequent ring closure of the resulting anion generates the ring system.^{70,71} Generally, the prerequisite for the formation of cyclopropanes from this type of transformation is that the carbon nucleophile contains a leaving group, or antecedent leaving group directly attached to the nucleophilic carbon. This is particularly true for the asymmetric methods of cyclopropane construction.⁷²

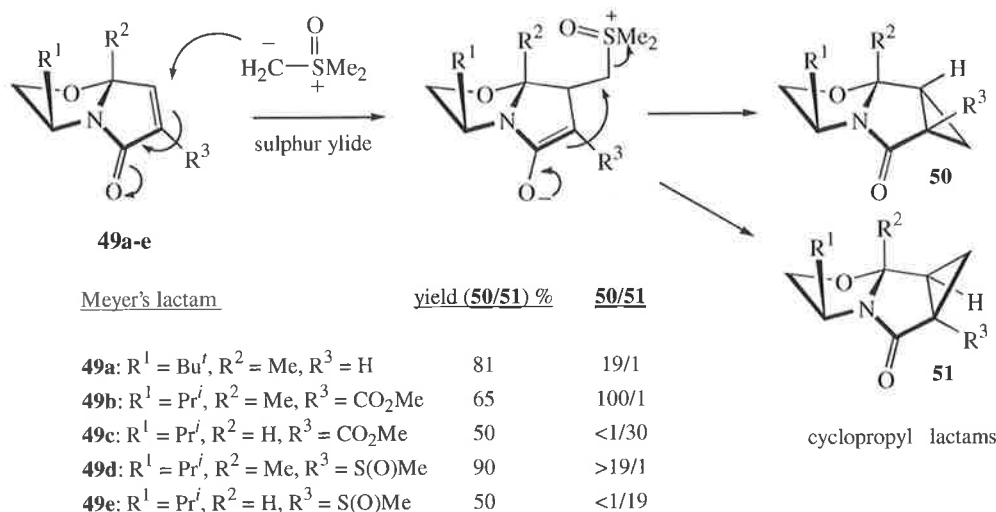
Scheme 13



Although there are many methods for cyclopropanation under the MIRC heading, comparatively few are useful for the asymmetric synthesis of cyclopropanes. Of these methods there are two classes of reaction (i) reagent-controlled and (ii) substrate-controlled.⁷² Comparatively little success has been forthcoming in reagent-controlled reactions. These are typified by reactions using chiral sulfonium, sulfoxonium, aminosulfoxonium and arsonium ylides as reagents on achiral α,β -unsaturated ketone and ester substrates. Most of these give very low ee and only moderate diastereoselectivities.⁷²

The substrate-controlled reactions rely upon essentially the same technique, however, this time achiral ylides, including phosphorus ylides, are allowed to react with chiral α,β -unsaturated substrates. An excellent example of this approach is the use of a chiral substrate known as a "Meyer's lactam" (**49a-e**), available from chiral amino alcohols.^{72,73} This enantio-pure compound directs the diastereomeric addition of sulphur ylides to generate cyclopropyl lactams of extremely high de in moderate to excellent chemical yield. Both diastereomers (**50**) and (**51**) are equally accessible by changing the substituent R^2 of the lactam (compare entries 2 to 3 and 4 to 5 in Scheme 14). Subsequent hydrolysis of the cyclopropyl lactam, generates the corresponding enantiomer in high ee.

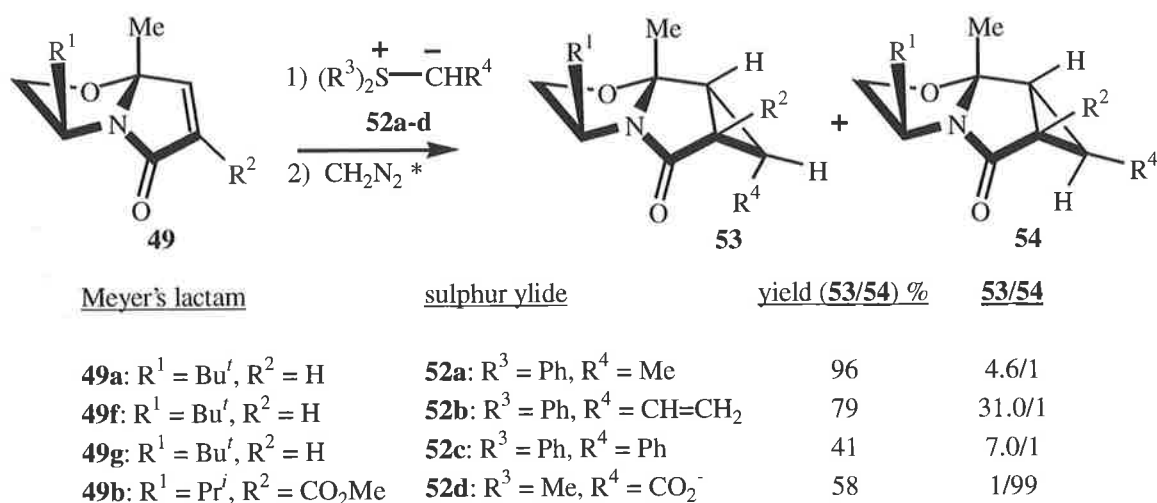
Scheme 14



similar reactions can be performed using $\text{Ph}_2\text{S}^+ \text{---} \text{C}^-$

There are many other examples of this type of substrate controlled chiral cyclopropane synthesis.⁷⁴⁻⁷⁶ However, these asymmetric reactions are limited to the addition of symmetrical units such as CH_2 and $\text{C}(\text{CH}_3)_2$ due to low ee obtained when using asymmetric groups. The Meyer's lactam, however, provides us with the one exception, Scheme 15.⁷²

Scheme 15



* Step 2) is only used in the case where $R = \text{CO}_2^-$ to immediately transform the cyclopropyl acids into their corresponding methyl esters.

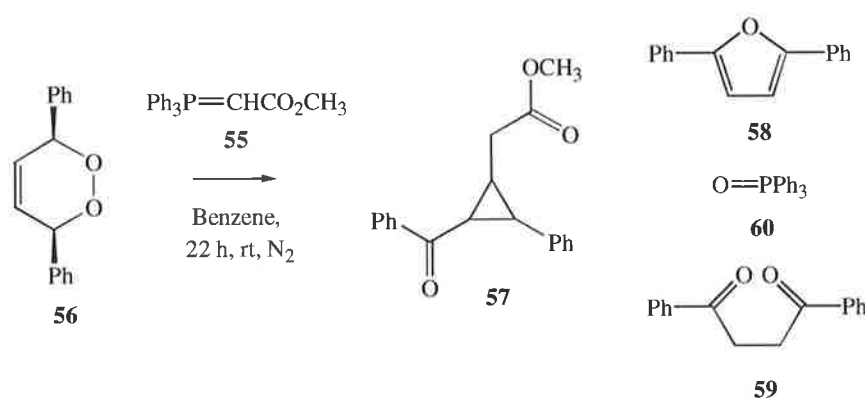
Overall, it has been shown that there are limitations to what can be achieved in the asymmetric synthesis of enantiomerically-pure cyclopropanes. There are many outstanding methods for the synthesis of 1,2-disubstituted cyclopropanes, however, there is a severe lack in methodology for the synthesis of enantiomerically-pure 1,2,3-trisubstituted cyclopropanes.

This thesis outlines two novel cyclopropanation reactions for the generation of 1,2,3-trisubstituted cyclopropanes from 1,2-dioxines and stabilised phosphorus ylides. Contained in the section below, is the history leading up to the discoveries detailed within this thesis.

Previous Research

Products resulting from 1,2-dioxines, (also known in the literature as endoperoxides and epiperoxides), and stabilised phosphorus ylides were first reported in a study by *Tanya Rathbone*.⁷⁷ Work within her Honours thesis she detailed the reaction of the stabilised phosphorus ylide (**55**) with an excess of 1,2-dioxine (**56**) in benzene. Cyclopropane (**57**) was reportedly isolated as the minor product, with the majority being decomposition products of the 1,2-dioxine, namely 2,5-diphenyl furan (**58**) and 1,4-diphenyl-1,4-butanedione (**59**); TPPO (**60**) was also isolated from the reaction mixture, Scheme 16.

Scheme 16

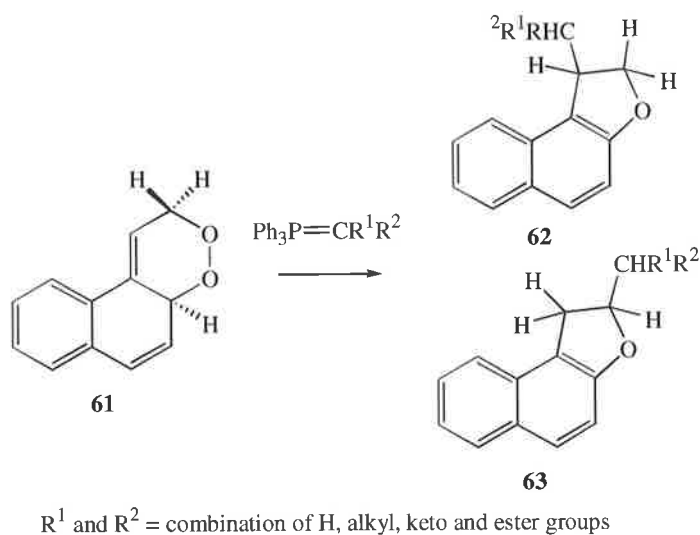


Due to time constraints optimisation of the reaction and elucidation of the stereochemistry of the cyclopropane was not carried out.

Research into the interaction of 1,2-dioxines and stabilised phosphorus ylides was continued in a study by *Tom Haselgrove*.⁷⁸ Work within his Honours thesis described a reproduction of the initial cyclopropanation reaction, which resulted in improvement of the yield and confirmation of the reliability of the transformation although the relative stereochemistry was yet to be determined.

Tom Haselgrove did, however, extend the general scope of the reaction to include 2,4a-dihydronaphtho[2,1-c][1,2]dioxines (**61**) which upon reaction with stabilised phosphorus ylides yield 1,2-dihydronaphtho[2,1-b]furans (**62**) and (**63**), Scheme 17.⁷⁸ Due to time constraints investigations into the broad scope and mechanistic details of this reaction were not carried out until a study by *Martyn Jevric*.⁷⁹ The mechanistic details of this reaction parallel and relate to those for the cyclopropanation reactions that are described in detail in the body of this thesis.

Scheme 17



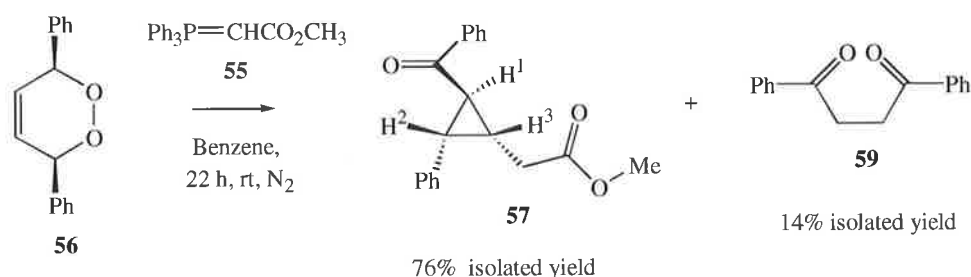
Research into cyclopropane formation was further continued in my Honours thesis which was directed at optimising the novel cyclopropanation reaction and determining the scope of the reaction and its mechanism.⁸⁰ The findings of my Honours thesis are discussed

below as they provide a suitable platform from which the further studies contained within this thesis evolved.

Cyclopropane structure

Initially, the procedure outlined by *Tom Haselgrove* was repeated and the cyclopropane (**57**) was isolated in 76% yield.⁷⁸ An extensive NMR study was then performed on the cyclopropane revealing the stereochemistry to be that shown in Scheme 18.

Scheme 18

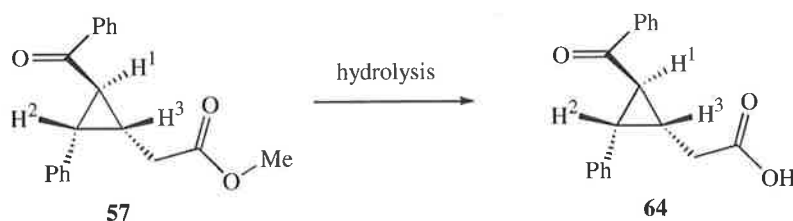


Connectivity and relative stereochemistry was determined by a series of one- and two-dimensional NMR experiments (^1H , ^{13}C , gCOSY, gHMBC, gHSQC and ROESY) whilst further confirmation of this connectivity came from IR analysis of cyclopropane (**57**). An aryl ketone generally will exhibit an absorption of between 1700 and 1685 cm^{-1} whilst an aryl ketone directly attached to a cyclopropyl ring will exhibit absorption of between 1670 and 1660 cm^{-1} .⁸¹ An unsaturated ester will typically exhibit absorption within the range $1750 - 1735\text{ cm}^{-1}$ and with the ester directly attached to the cyclopropane the ester will absorb within the range $1730 - 1715\text{ cm}^{-1}$.⁸¹ Two absorptions were obtained for cyclopropane (**57**) at 1738 and 1657 cm^{-1} indicating that it is the ketone moiety that is attached directly to the cyclopropane ring and not the carbonyl of the ester moiety.

The relative stereochemistry was assigned utilising the magnitudes of the couplings of cyclopropyl protons H^1 , H^2 and H^3 . Typical *trans* couplings between 4.0 and 9.5 Hz and typical *cis* couplings between 7.0 and 13.0 Hz were observed.^{81,82} Examination of ^1H NMR spectra revealed the magnitudes of $^3J_{1-2}$ and $^3J_{1-3}$ to be 4.8 Hz indicating a *trans*

relationship to both H^2 and H^3 . H^2 exhibited couplings $^3J_{2-1} = 4.8$ Hz and $^3J_{2-3} = 9.2$ Hz indicating that H^2 was *trans* to H^1 and has a *cis* relationship to H^3 .

Scheme 19



Subsequent X-ray analysis of the parent acid of (**57**) unambiguously confirmed the structure to be that assigned by NMR spectroscopy, Appendix 1.⁸⁰ X-ray analysis of other unhydrolysed cyclopropyl derivatives, showed that no isomerisation of cyclopropane (**57**) occurred during the hydrolysis reaction, Appendix 1.

Optimisation of cyclopropane yield

Solvent effect studies determined that dichloromethane was the optimal solvent for the cyclopropanation, Scheme 18, with the reaction proceeding to completion over three days with minimal production of the 1,4-dicarbonyl byproduct (**59**), Table 1.

Table 1. The Effect of Solvent on the Rate of Reaction Between 1,2-Dioxine (56**) and Stabilised Ylide (**55**), and Cyclopropane (**57**) : 1,4-Dicarbonyl (**59**) Ratio at 25 °C.**

entry	solvent	relative rate	ratio 55c : 58a (%)
1	CH ₂ Cl ₂	0.6	97 : 3
2	CCl ₄	0.9	92 : 8
3	benzene	1.0	82 : 18
4	CH ₃ CN	8.0	89 : 11

Scope of reaction

Now with a convenient and high yielding procedure established, the scope of reaction was explored. A series of experiments were performed in order to ascertain the types of 1,2-dioxines and stabilised phosphorus ylides able to undergo the cyclopropyl transformation, Scheme 20.

Scheme 20

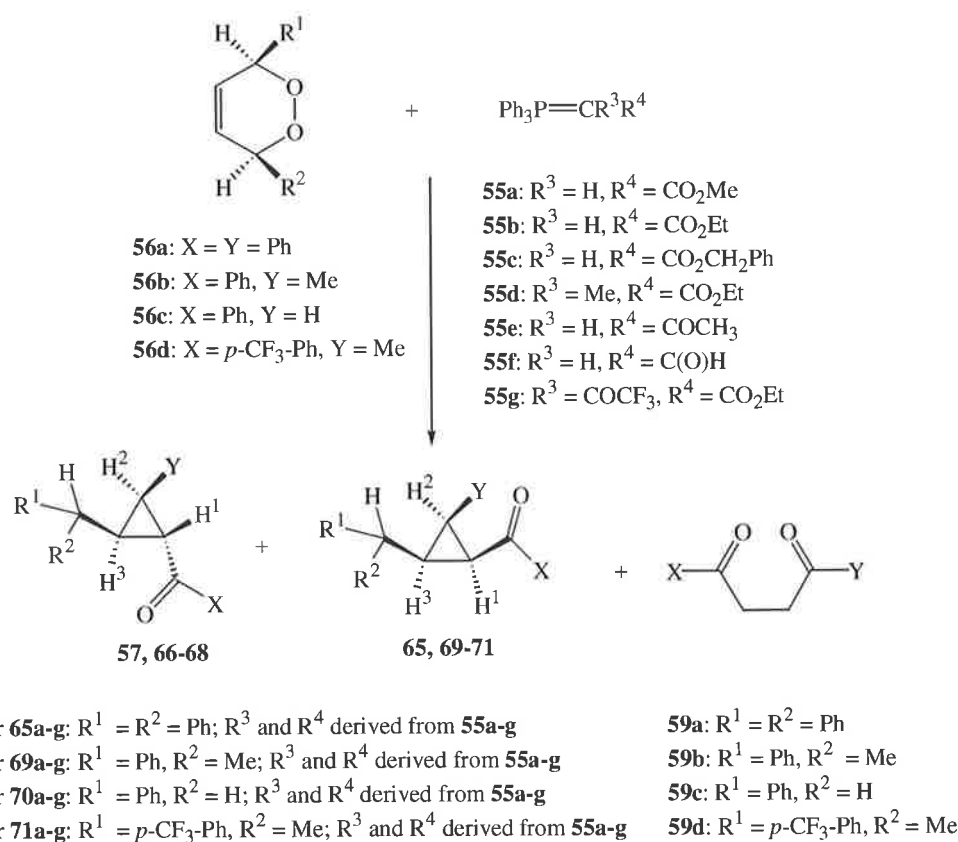
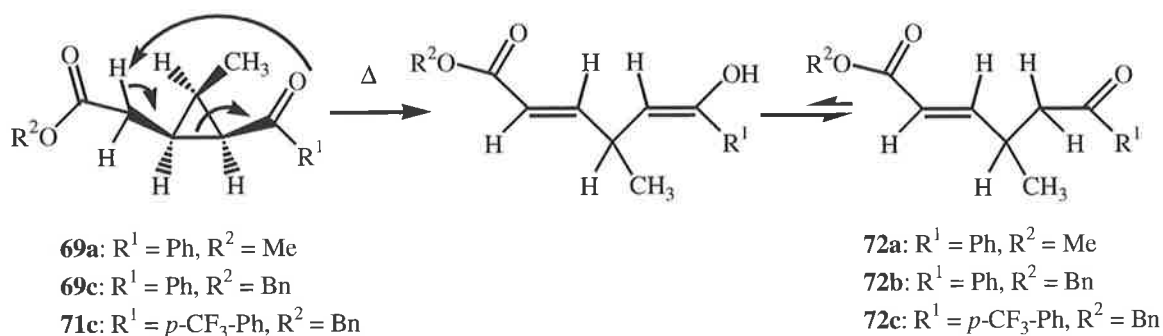


Table 2. Reaction of 1,2-Dioxines (56a-d) and Stabilised Phosphorus Ylides (55a-g).

entry	1,2-dioxine	ylide	completion time (days)	product(s); yields (%)
1	56a	55a	3	57a ; (96), 59a ; (4)
2		55b		57b ; (96), 59a ; (4)
3		55c		57c ; (97), 59a ; (3)
4		55d		57d ; (41), 59a ; (52)
5		55e		59a ; (100)
6		55f		59a ; (100)
7		55g		58a ; (100)
8	56b	55a	7	66a ; (82), 69a ; (18)
9		55c		66c ; (85), 69c ; (15)
10		55e		complex mixture
11	56c	55c	1	67c ; (100)
12		55g		-
13	56d	55c	1	68c ; (82), 71c ; (18)

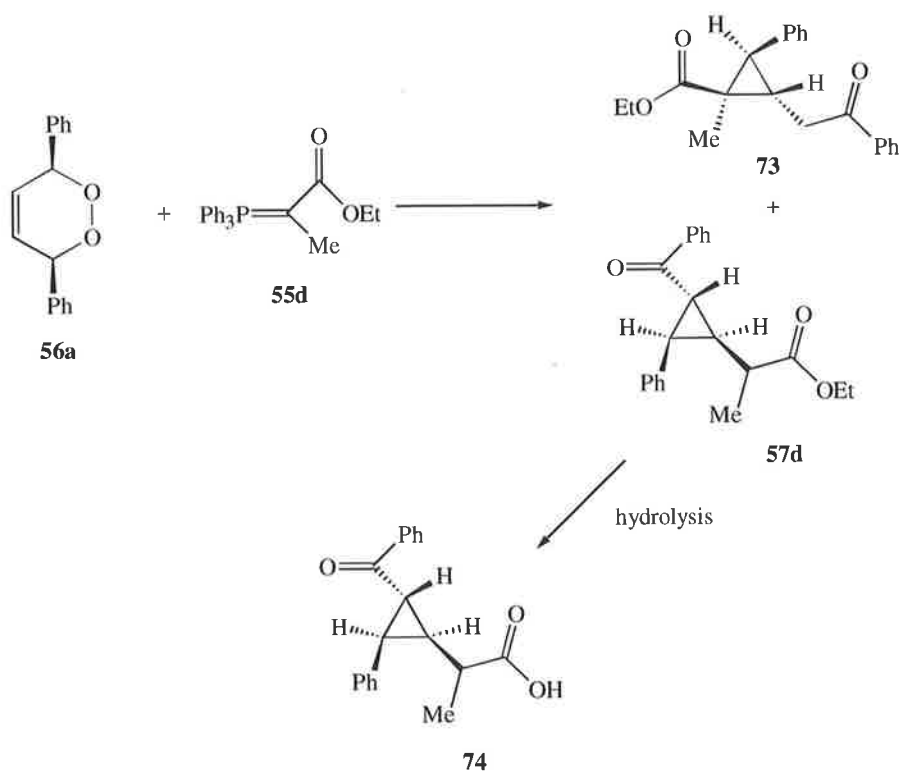
It was subsequently determined that the cyclopropanation reaction proceeded in high yields for all mono-substituted stabilised ester ylides and all 1,2-dioxines tested. Particularly high diastereomeric excess was observed with the use of 1,2-dioxines (**56a**) and (**56c**). However, the de was reduced when 1,2-dioxines (**56b**) and (**56d**) were employed, with the isolation of another cyclopropyl diastereomer (**69a**, **69c** and **71c**). These unstable cyclopropyl isomers were determined to have an all-*cis* configuration of substituents by extensive ^1H and ^{13}C , one- and two-dimensional NMR spectroscopy and also by characterisation of their rearrangement products, Scheme 21.

Scheme 21

The enolene rearrangement or homodienyl[1,5] sigmatropic hydrogen shift,^{83,84} in the case of the all-*cis* cyclopropyl isomers (**69a**, **69c** and **71c**) is extremely facile at elevated temperatures, however, occurs slowly at room temperature. Increasing the temperature to 60 °C afforded quantitative rearrangement of cyclopropanes (**69a**, **69c** and **71a**) to their corresponding α,β -unsaturated esters (**72a-c**), Scheme 21. The fact that this rearrangement occurs also supports assignment of an all-*cis* configuration for cyclopropanes (**69a**), (**69c**) and (**71a**).

The doubly substituted ylide (**55d**) was also shown to produce cyclopropane (**57d**), although in only moderate yield, demonstrating that it is possible to generate a fourth stereogenic centre within the cyclopropane products, Scheme 22.

Scheme 22



^1H NMR and X-ray crystallographic analysis of the parent acid (**74**) showed that this centre was of one configuration only, Appendix 2. A small amount (7%) of another cyclopropyl isomer was also detected and tentatively assigned as ethyl 1-methyl-2-(2-

oxo-2-phenylethyl)-3-phenyl-1-cyclopropanecarboxylate (**73**). This later product will become important to the studies discussed in Chapter 5.

In the case of the keto- (**55e**) and aldo- (**55f**) stabilised ylides, no cyclopropane was obtained, instead either the 1,4-dicarbonyl byproduct or a complex mixture of products was formed, indicating that these types of ylides were unsuitable for cyclopropanation. Ylides such as (**55g**) were also unsuitable due to the high degree of stabilisation of the ylide carbanion and probably to some extent, the steric bulk of the ylide. Reactions involving ylide (**55g**) resulted in no reaction at room temperature, however, on heating the 1,2-dioxine was transformed into the corresponding furan (**58a**). Furan formation in this manner was previously reported by *Tanya Rathbone*.⁷⁷

It is worth mentioning at this point that it was noticed that the rates of cyclopropanation varied considerably between the four 1,2-dioxines (**56a-d**) used in the study. This is shown by comparison of entries 10 and 14 from Table 2 in which the incorporation of an electron-withdrawing group shows a seven-fold increase in the rate of cyclopropanation. The results indicated that the presence of the electron-withdrawing group was increasing the rate of the rate-determining step. The rds was later proposed to be the removal of the most acidic proton α to the oxygen-oxygen linkage of the 1,2-dioxine by the ylide acting as a mild base. Consequently, the presence of an electron-withdrawing group adjacent the α proton, results in an increase in the acidity of the proton α to the oxygen-oxygen linkage, thus, allowing the proton to be more readily removed by the ylide.

Additive effects and ³¹P NMR

The effect of additives on cyclopropane formation was evaluated, in order to further explore the mechanism of the cyclopropane transformation. Table 3 outlines the experiments undertaken.

Table 3. Effect of Additives and Temperature on the Reaction Between 1,2-Dioxine (56a) and Ylide (55c), and Cyclopropane (57c) : 1,4-Dicarbonyl (59a) Ratio.

entry	additive	ratio 57c : 59a (%)
1	TEMPO (1 equiv.)	78 : 22
2	H ₂ O (10 equiv.)	83 : 17
3	cyclohexene (3 equiv.)	85 : 15
4	TPP (0.5 equiv.)	73 : 27

TEMPO also known as 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical was added to the reaction to inhibit any radical chain reactions that might be occurring as part of the cyclopropanation mechanism. As can be seen from entry 1 the ratio of cyclopropane to 1,4-dicarbonyl was unaffected indicating that the mechanism does not involve free radical intermediates.

It is known in the literature that zwitterionic phosphorus intermediates are highly susceptible to hydrolysis by water.⁸⁵ However, the addition of water to the cyclopropanation reaction had no effect on the product ratio indicating that no intermediacy or formation of zwitterionic phosphorus intermediates occurs within the reaction mechanism.

Cyclohexene is a known carbene trap and if the mechanism of cyclopropanation proceeded via carbene addition competition for the free carbene by cyclohexene would be expected.⁸⁶ No change in product ratio or formation of cyclopropyl-cyclohexane was observed, indicating that the reaction does not proceed via a carbene mechanism. Furthermore, corroboration of this result was found through the observation that TPP was not liberated during cyclopropanation as determined by ³¹P NMR monitoring of the reaction. This would be expected in the event of free carbene formation from an ylide source.^{86,87}

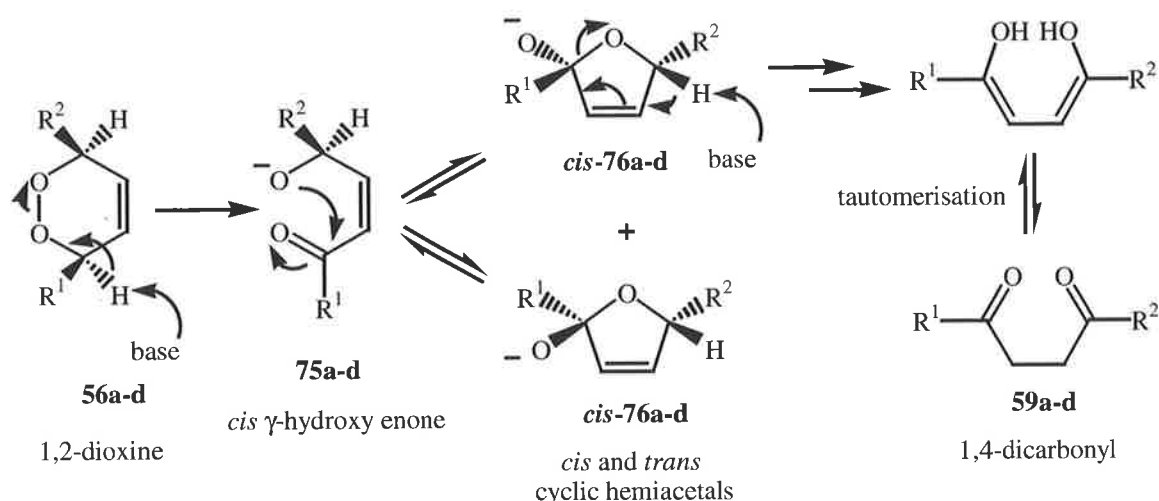
TPP was added to the reaction to determine whether free TPP was responsible for the presence of the 1,4-dicarbonyl byproduct in the first instance. This premise was arrived upon as it is known that TPP can insert itself into the oxygen-oxygen linkages of 1,2-dioxolanes⁸⁸ and dioxetanes⁸⁹. Although TPP did lead to an increase in the proportion of

1,4-dicarbonyl (**58a**) it has since been shown by ^{31}P NMR that no free TPP is present during the reaction. In fact, ^{31}P NMR monitoring of the reaction revealed no phosphorus intermediates, only an increase in TPPO with concomitant decrease of ylide as cyclopropane was formed. It was also noted from these experiments that all of the ylide (1 eq in relation to 1,2-dioxine) was not completely consumed during the reaction. The amount left over corresponded to the amount of 1,4-dicarbonyl byproduct formed in the reaction. Hence the 1,4-dicarbonyl byproduct is being formed catalytically.

1,4-Dicarbonyl formation

Formation of the 1,4-dicarbonyl byproduct was found to be the result of a Kornblum-de la Mare decomposition. It was noted by Balci *et al.* that cyclic peroxides on treatment with bases such as TEA undergo rearrangement to their corresponding dicarbonyls.⁹⁰ Applying this rearrangement to 1,2-dioxines of the type used in this thesis leads to the following proposed mechanism for 1,4-dicarbonyl formation, Scheme 23. The reaction is initiated via the removal of the most acidic proton α to the oxygen-oxygen linkage of the 1,2-dioxine. This is then followed by formation of *cis* and *trans* cyclic hemiacetals, which when deprotonated, ring-open and tautomerise affording the 1,4-dicarbonyl product, Scheme 23.⁹⁰

Scheme 23



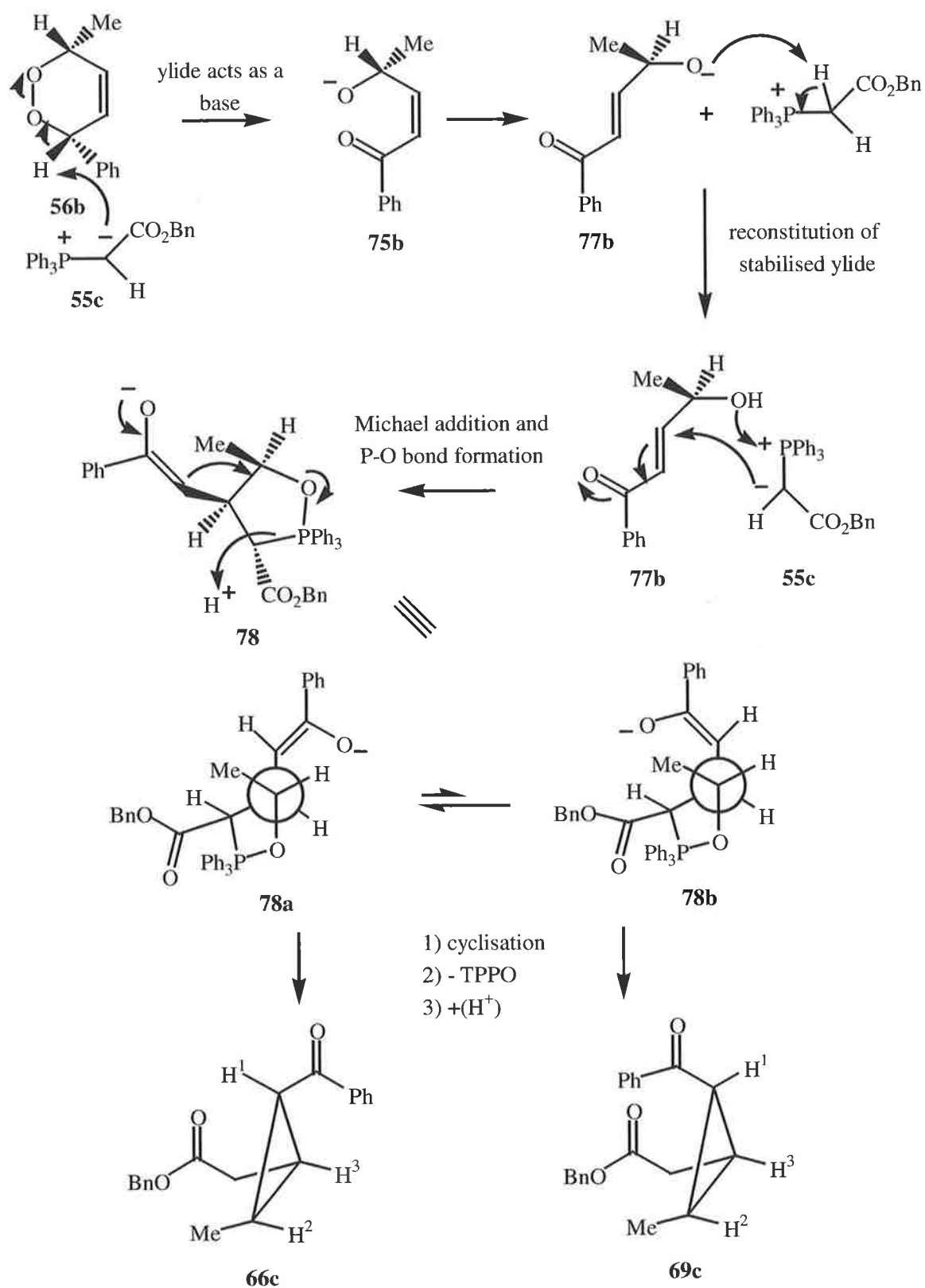
It was found that 1,2-dioxines (**56a-d**) proceeded quantitatively to 1,4-dicarbonyl compounds (**59a-d**) on treatment with 10 equivalents of TEA. Therefore, all evidence at this time suggested that it was the basic nature of the stabilised phosphorus ylide that led to the formation of the 1,4-dicarbonyl byproducts during cyclopropanation.

Formation of intermediate *trans* γ -hydroxy enones

Following the reaction of 1,2-dioxine (**56b**) and ylide (**55c**) by ^1H NMR revealed the presence of a small proportion of *trans* γ -hydroxy enone (**77b**) (1-2%), Scheme 24. Isolation of the *trans* γ -hydroxy enone (**77b**) from the reaction mixture and addition of ylide (**55c**) yielded cyclopropanes (**66c**) and (**69c**), however, in a lower yield compared to the reaction starting from 1,2-dioxine (**56b**). Further elaboration on the use of *trans* γ -hydroxy enones in the synthesis of cyclopropanes was prevented due to time constraints. This significant finding, however, allowed the proposition of an initial MIRC mechanism for the formation of both cyclopropane isomers, Scheme 24.

Utilising a specific example to illustrate, it was postulated at this stage that the ylide (**55c**) acted as a weak base⁸⁶ removing the most acidic proton α to the oxygen-oxygen linkage of the 1,2-dioxine (**56b**) causing rearrangement into the *trans* γ -hydroxy enone (**77b**) with regeneration of the stabilised ylide. Concomitant Michael addition of the ylide to the *trans* γ -hydroxy enone with oxygen-phosphorus bond formation results in the generation of the oxaphospholane intermediate **78**. Cyclisation of enolate of **78** and expulsion of TPPO resulted in the formation of both cyclopropyl isomers (**66c** and **69c**) the ratio of which depended upon the orientation of enolate collapse. It is the unfavorable interactions, which dictate that the equilibrium of **78a** and **78b** should lie toward the isomer with the bulk of the enolate moiety rotated away from the methyl group.

Scheme 24



In summation, it was shown that a range of 1,2-dioxines can undergo cyclopropanation with stabilised ester phosphorus ylides in high yield and high diastereomeric excess. A crucial intermediate was uncovered in the form of *trans* γ -hydroxy enones, which led to the postulation of an initial Michael addition mechanism.

The investigations discussed within this thesis begin where this previous research finished, with the synthesis of *trans* γ -hydroxy enones and the mechanistic studies of their interactions with stabilised phosphorus ylides.

Chapter 2: *trans* γ -Hydroxy Enones

Introduction

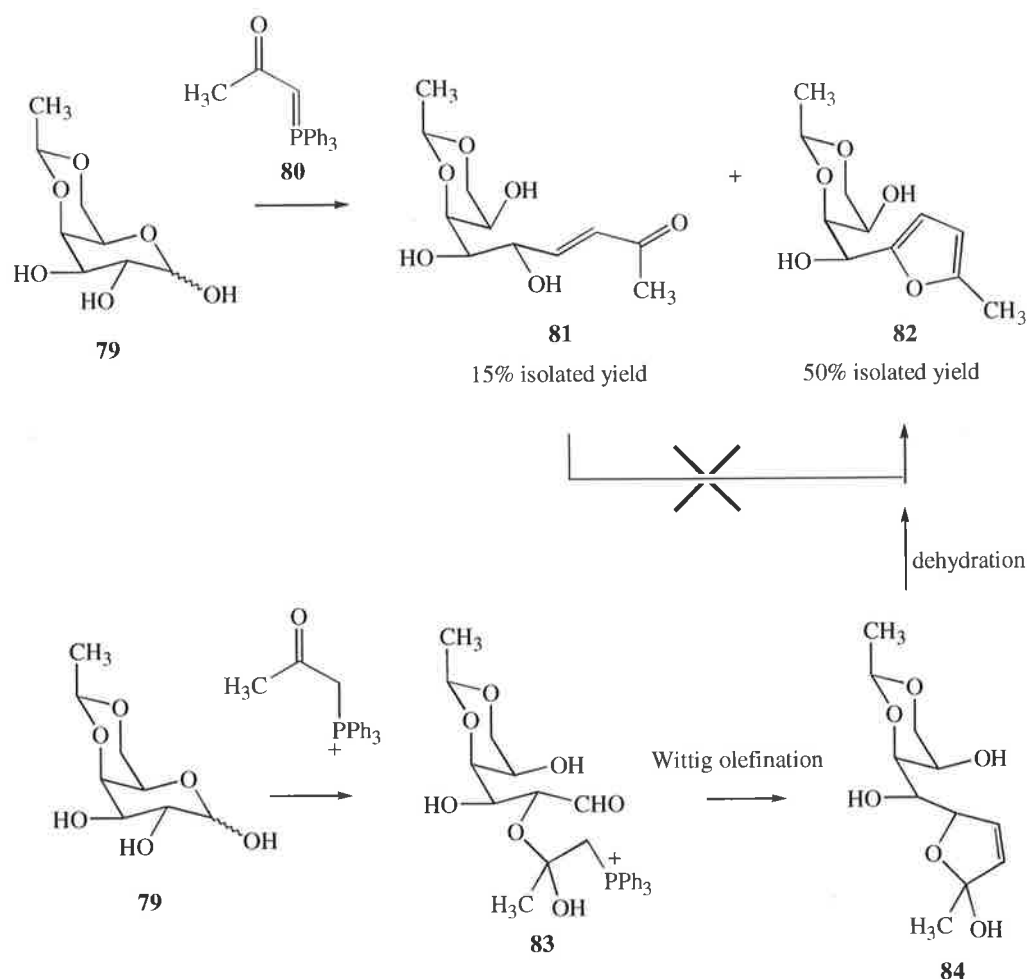
trans γ -Hydroxy enone (**77b**) and its subsequent reaction with ylide (**55c**) to yield cyclopropanes (**66c**) and (**69c**), has previously been demonstrated, Scheme 24. This finding prompted an investigation into the synthesis of *trans* γ -hydroxy enones and their involvement in cyclopropanation proceeding from 1,2-dioxines and stabilised phosphorus ylides.

Examples of *trans* γ -hydroxy enone construction are relatively rare in the literature, which is predominantly due to their inherent instability (*vide infra*). Five strategies for the synthesis of *trans* γ -hydroxy enones exist, these are, (i) the coupling of stabilised phosphorus ylides to α -hydroxy aldehydes; (ii) the coupling of sulfoxides and aldehydes; (iii) the coupling of organotin reagents and acid chlorides; (iv) the decomposition of β,γ -epoxy ketones and (v) palladium mediated decomposition of 1,2-dioxines.

Coupling of stabilised phosphorus ylides to α -hydroxy aldehydes

The sole literature example for the coupling of stabilised phosphorus ylides and α -hydroxy aldehydes involves the galactose derivative (**79**) which when allowed to react with ylide (**80**) gave rise to *trans* γ -hydroxy enone (**81**) and furan (**82**), Scheme 25.⁹¹

Scheme 25



Interestingly, an unusual intramolecular Wittig reaction is proposed for the formation of furan (**82**) as treatment of (**81**) under the conditions of the original reaction reportedly did not lead to furan (**82**) formation. The conjugate acid of ylide (**80**) supposedly undergoes hemiketalisation with the hydroxyl group adjacent the anomeric center of sugar (**79**) to generate (**83**). Species (**83**) is then deprotonated to generate an ylide, which undergoes intramolecular Wittig olefination to yield (**84**); dehydration of (**84**) yields furan (**82**), Scheme 25.

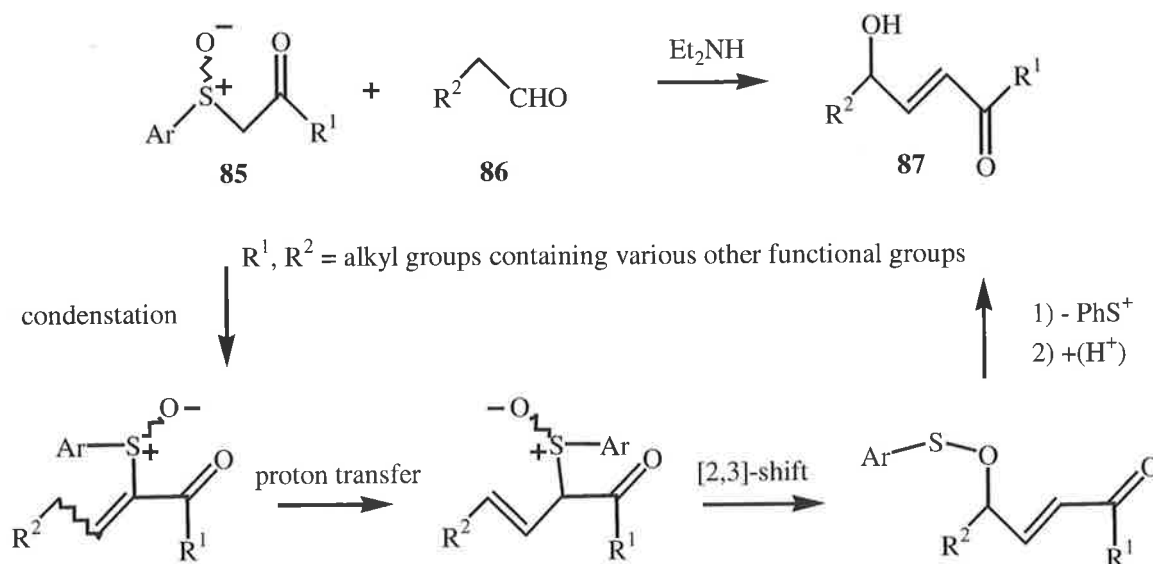
This method for synthesising *trans* γ -hydroxy enones has been used by *Francine Palmer* successfully in parallel to this research.⁹² *Francine's* work on the interaction of stabilised phosphorus keto ylides and chiral α -hydroxy aldehydes has enabled the synthesis of enantiomerically-enriched *trans* γ -hydroxy enones and subsequently enantio-enriched

cyclopropanes. Examples of this reaction being used to synthesise *trans* γ -hydroxy α,β -unsaturated esters are also known.^{93,94}

Coupling of sulfoxides and aldehydes

Recently the technique of sulfoxide and aldehyde coupling for the synthesis of *trans* γ -hydroxy enones⁹⁵ has received considerable attention.⁹⁶⁻⁹⁸ Through this methodology β -keto sulfoxides (**85**) and various aldehydes (**86**) have been used to generate a host of alkyl substituted *trans* γ -hydroxy enones (**87**), Scheme 26.

Scheme 26



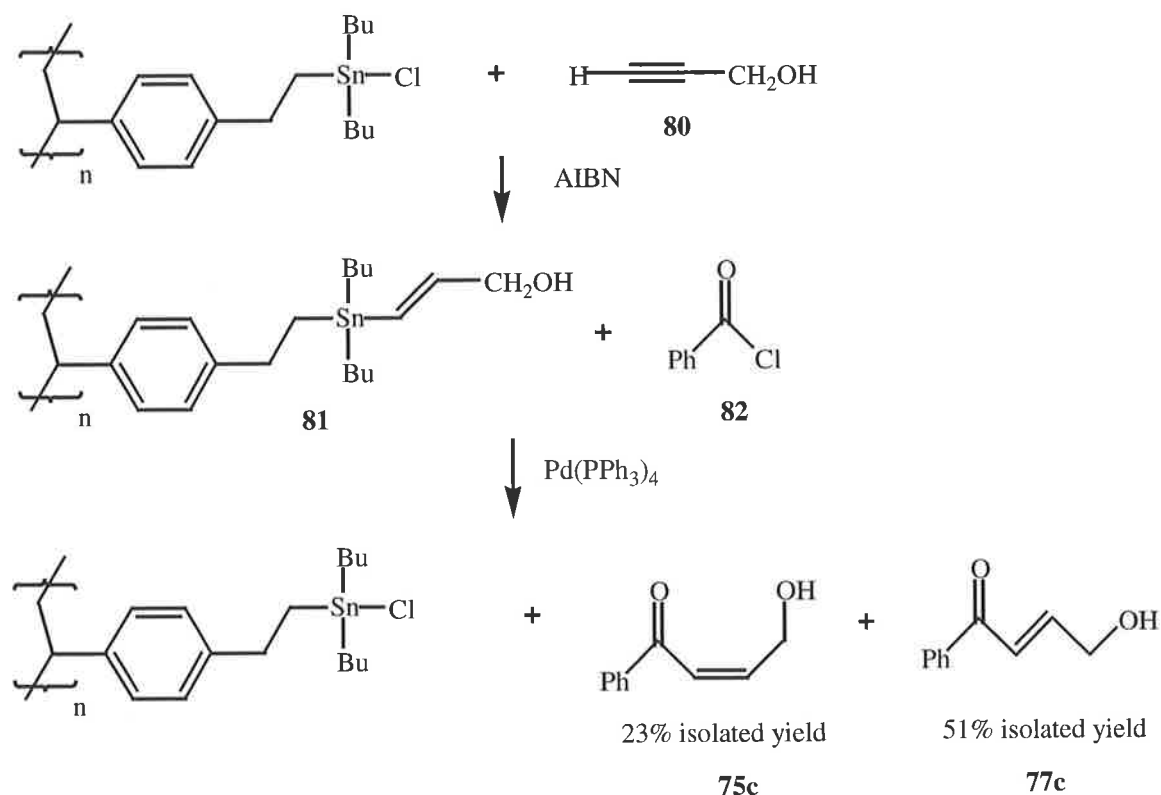
The potential of this method for the chiral synthesis of *trans* γ -hydroxy enones has been demonstrated by the synthesis of enantio-enriched *trans* γ -hydroxy α,β -unsaturated esters utilising enantio-enriched sulfoxides.⁹⁹ However, this methodology has not been used for the synthesis of aryl substituted *trans* γ -hydroxy enones.

Coupling of organotin reagents and acid chlorides

The use of polymer supported organotin reagents demonstrates another method for the

synthesis of *trans* γ -hydroxy enones.¹⁰⁰ As outlined in Scheme 27 the organotin reagent (**89**) was generated via hydrostannation of terminal alkyne (**88**). The resultant organotin reagent (**89**) was then subjected to a Stille reaction (palladium-catalysed cross-coupling reaction of organotin reagents), in which it was coupled to the acid chloride (**90**). The resulting *cis* (**75c**) and *trans* (**77c**) γ -hydroxy enones were obtained in a 31 : 69 ratio respectively.

Scheme 27

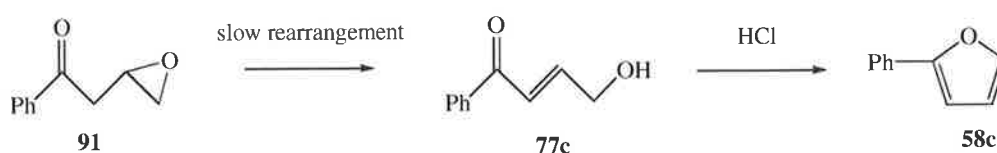


Decomposition of β,γ -epoxy ketones

trans γ -Hydroxy enone (**77c**) as described in the previous example was also found to be the decomposition product of epoxide (**91**).¹⁰¹ Upon standing it was discovered that epoxide (**91**) underwent slow decomposition into *trans* γ -hydroxy enone (**77c**), Scheme 28. Characterisation of this compound was carried out using IR, UV and ^1H NMR spectroscopic techniques. However, Coxon *et al.* was unable to determine the stereochemistry of their isolated product. Upon examination of the spectral data and

comparison with *trans* γ -hydroxy enone (**77c**) and *cis* γ -hydroxy enone (**75c**) synthesised during the course of this research, it is certain that the *trans* isomer was obtained. Treatment of the isolated *trans* γ -hydroxy enone (**77c**) with a trace amount of hydrochloric acid resulted in quantitative transformation into 2-phenylfuran (**58c**). No mechanism was put forward for the decomposition of epoxide (**91**) or *trans* γ -hydroxy enone (**77c**), probably as a result of ambiguity about the *cis* / *trans* orientation of the olefin moiety.

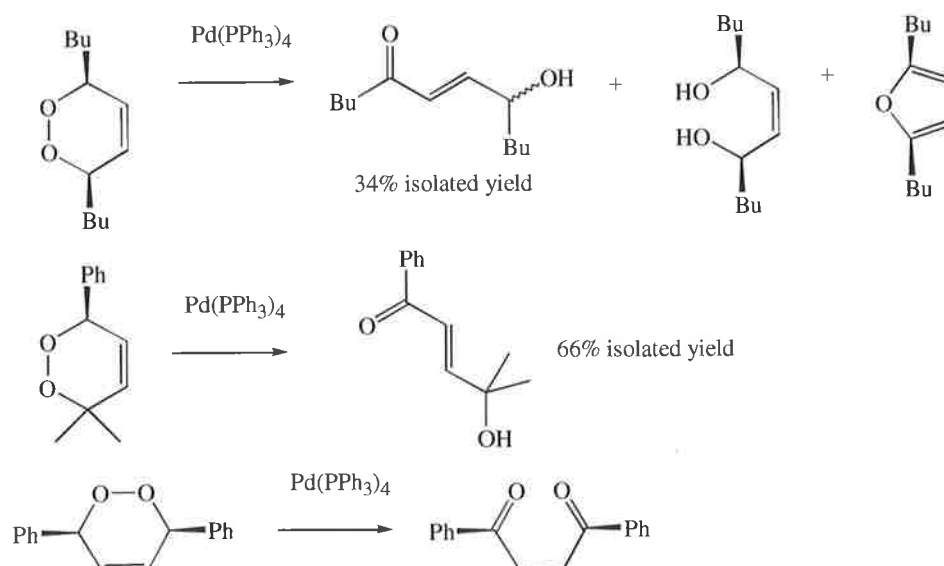
Scheme 28



Palladium mediated decomposition of 1,2-dioxines

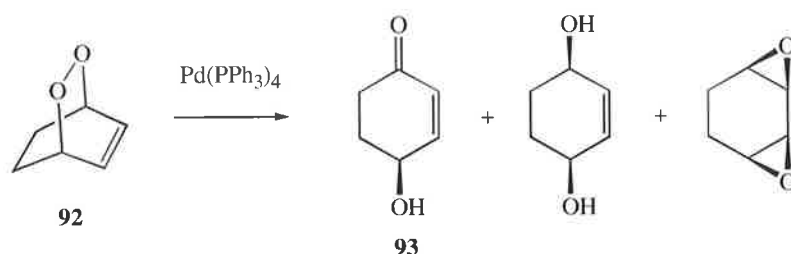
The final method for the formation of *trans* γ -hydroxy enones is via Pd(0) catalysed rearrangement of 1,2-dioxines.¹⁰² Treatment of 1,2-dioxines of the type shown in Scheme 29 with Pd(PPh₃)₄ resulted in the formation of either *trans* γ -hydroxy enones, diols, furans, or 1,4-dicarbonyl compounds.

Scheme 29



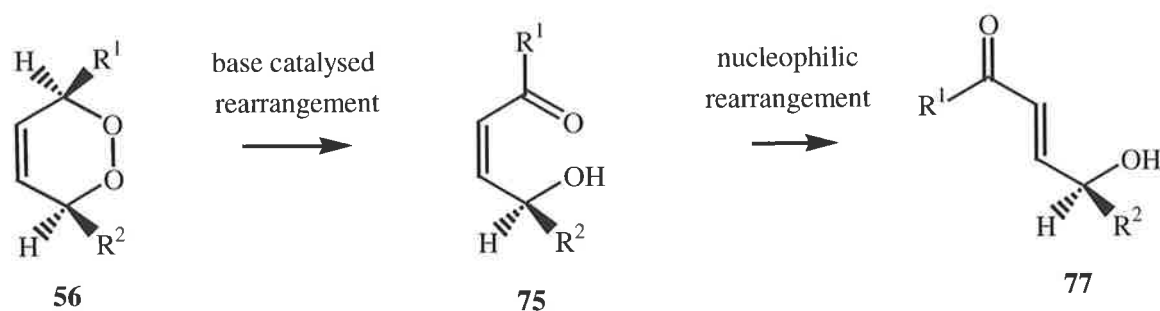
These products may also arise from the *cis* γ -hydroxy enones, which are the proposed precursors to the *trans* γ -hydroxy enones in these reactions. Scheme 30 shows the formation of *cis* γ -hydroxy enone (**93**) resulting from treatment of bicyclic peroxide (**92**) under identical reaction conditions to the examples in Scheme 29. This provides support for the hypothesis that the *trans* γ -hydroxy enones are arising from their isomeric *cis* γ -hydroxy enones.¹⁰²

Scheme 30



For the synthesis of the *trans* γ -hydroxy enones desired for research into the formation of cyclopropanes from 1,2-dioxines and stabilised phosphorus ylides, the palladium catalysed rearrangement of 1,2-dioxines demonstrates the most appropriate methodology. This methodology, however, generated a range of other products, and demonstrates utility only in the rearrangement of symmetrical 1,2-dioxines or 1,2-dioxines containing only one proton α to the oxygen-oxygen linkage.¹⁰² A method was required to accommodate the rearrangement of unsymmetrical 1,2-dioxines of the type previously utilised for the construction of cyclopropanes.⁸⁰ Previously it was demonstrated that *trans* γ -hydroxy enone (**77b**) could be isolated from the reaction of 1,2-dioxine (**56b**) and ylide (**55c**) (as described in Chapter 1) as a consequence of a base catalysed rearrangement. It was envisaged then, that base catalysed rearrangement (using a simple base such as TEA) of 1,2-dioxines into *cis* γ -hydroxy enone via regioselective deprotonation followed by base catalysed nucleophilic isomerisation, would lead to the formation of *trans* γ -hydroxy enone, Scheme 31.

Scheme 31

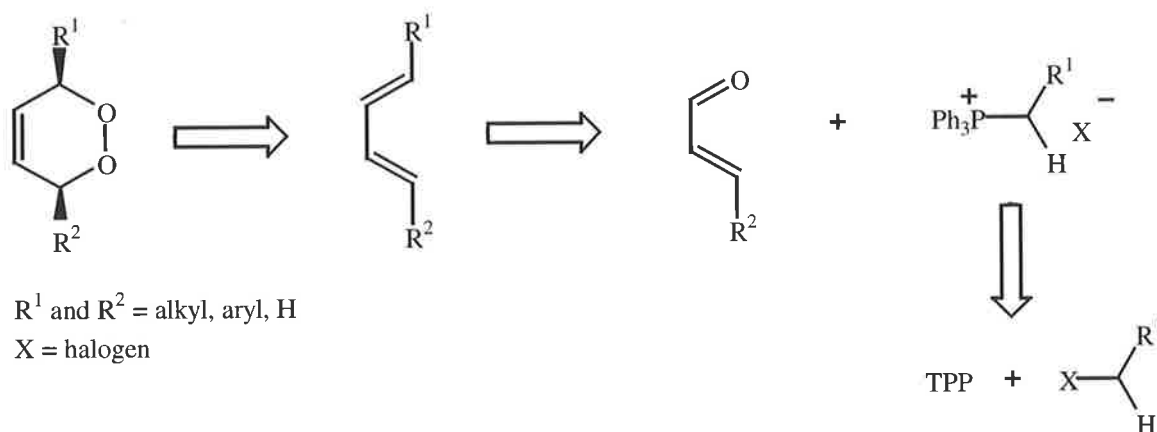


Results and Discussion

Synthesis of 1,2-dioxines

1,2-dioxines utilised in the formation of *trans* γ -hydroxy enones and other compounds described throughout this thesis were synthesised according to the retro-synthetic procedure outlined in Scheme 32.

Scheme 32



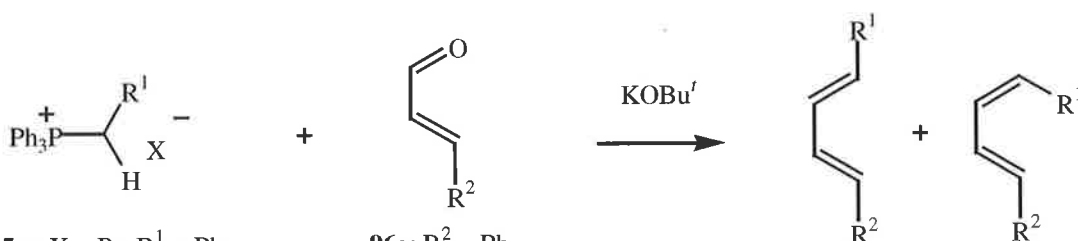
Synthesis of phosphonium salts (**95a-d**), proceeded in high yield via the combination of equi-molar amounts of primary halides (**94a-d**) and TPP, Scheme 31.¹⁰³

Scheme 33

**94a:** X = Br, R¹ = Ph**94b:** X = I, R¹ = H**94c:** X = Br, R¹ = *p*-CF₃-Ph**94d:** X = I, R¹ = Me**95a:** X = Br, R¹ = Ph**95b:** X = I, R¹ = H**95c:** X = Br, R¹ = *p*-CF₃-Ph**95d:** X = I, R¹ = Me

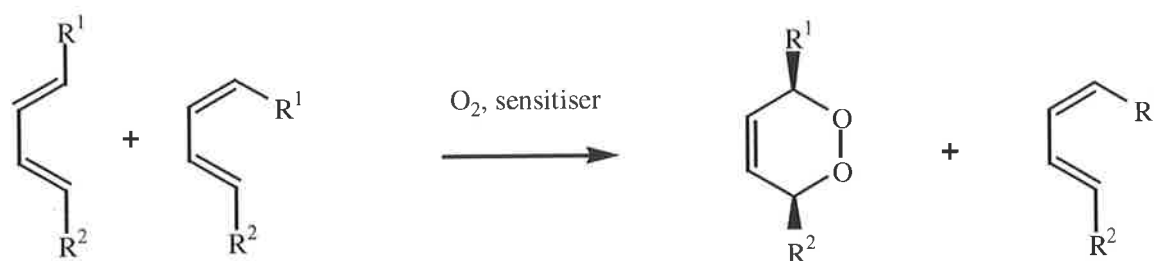
With successful synthesis of phosphonium salts (**95a-d**), the requisite 1,3-butadienes (**97b-e**) were synthesised via their combination with *trans*- α,β -unsaturated aldehydes (**96a-b**) in the presence of potassium *t*-butoxide, Scheme 34.¹⁰³ Synthesis of 1,3-butadienes (**97b-e**) resulted in the formation of two stereoisomers *trans-trans* and *cis-trans*. The mixture of isomers was utilised, without separation, in the formation of 1,2-dioxines and in all cases the *cis-trans* 1,3-butadiene was recovered unchanged from the reaction mixture.

Scheme 34

**95a:** X = Br, R¹ = Ph**95b:** X = I, R¹ = H**95c:** X = Br, R¹ = *p*-CF₃-Ph**95d:** X = I, R¹ = Me**96a:** R² = Ph**96b:** R² = Me**97b:** R¹ = Ph, R² = Me**97c:** R¹ = H, R² = Ph**97d:** R¹ = *p*-CF₃-Ph, R² = Me**97e:** R¹ = R² = Me

The 1,2-dioxines (**56a-e**) were synthesized by [4 π + 2 π] cycloaddition of singlet oxygen to the corresponding 1,3-butadienes (**97a-e**) under photolytic conditions in the presence of Rose Bengal, bis(triethylammonium)salt as the photosensitiser, Scheme 35.

Scheme 35



97a: $R^1 = R^2 = \text{Ph}$

97b: $R^1 = \text{Ph}, R^2 = \text{Me}$

97c: $R^1 = \text{H}, R^2 = \text{Ph}$

97d: $R^1 = p\text{-CF}_3\text{-Ph}, R^2 = \text{Me}$

97e: $R^1 = R^2 = \text{Me}$

56a: $R^1 = R^2 = \text{Ph}$

56b: $R^1 = \text{Ph}, R^2 = \text{Me}$

56c: $R^1 = \text{Ph}, R^2 = \text{H}$

56d: $R^1 = p\text{-CF}_3\text{-Ph}, R^2 = \text{Me}$

56e: $R^1 = R^2 = \text{Me}$

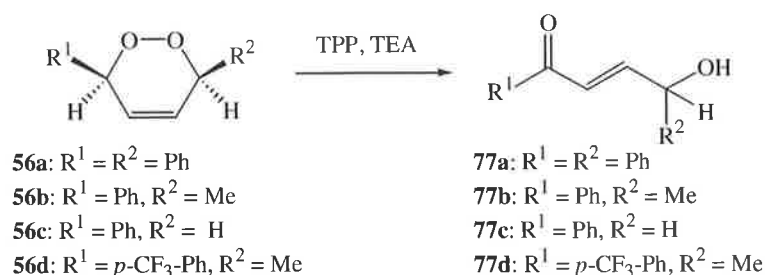
Synthesis of *trans* γ -hydroxy enones

With the 1,2-dioxines (**56a-d**) in hand it was found that upon TEA catalysed rearrangement of 1,2-dioxines at a much lower concentration than previously used (1 equivalent as opposed to 10), in dichloromethane at room temperature *trans* γ -hydroxy enones were generated. Competing, Kornblum-de la Mare rearrangement of the 1,2-dioxine to form 1,4-dicarbonyls, however, severely inhibited this methodology as an effective procedure.

It was discovered after much trial and error that the addition of TPP (0.5 equivalents) to 1,2-dioxine in the presence of TEA (1 equivalent) gave a far superior yield of the *trans* γ -hydroxy enones. This procedure was utilised to synthesise *trans* γ -hydroxy enones (**77a-d**) in isolated yields of between 77 - 95% as depicted in Scheme 36 and within Table 4.

trans γ -Hydroxy enones (**77a-d**) in their pure state were unstable, undergoing rearrangement at sub-ambient temperatures to generate their corresponding furans (**58a-d**) in quantitative yield.

Scheme 36

Table 4. Formation of *trans* γ -Hydroxy Enones (**77a-d**).^a

entry	1,2-dioxine	product; yield (%)
1	56a	77a ; (82)
2	56b	77b ; (95)
3	56c	77c ; (85)
4	56d	77d ; (77)

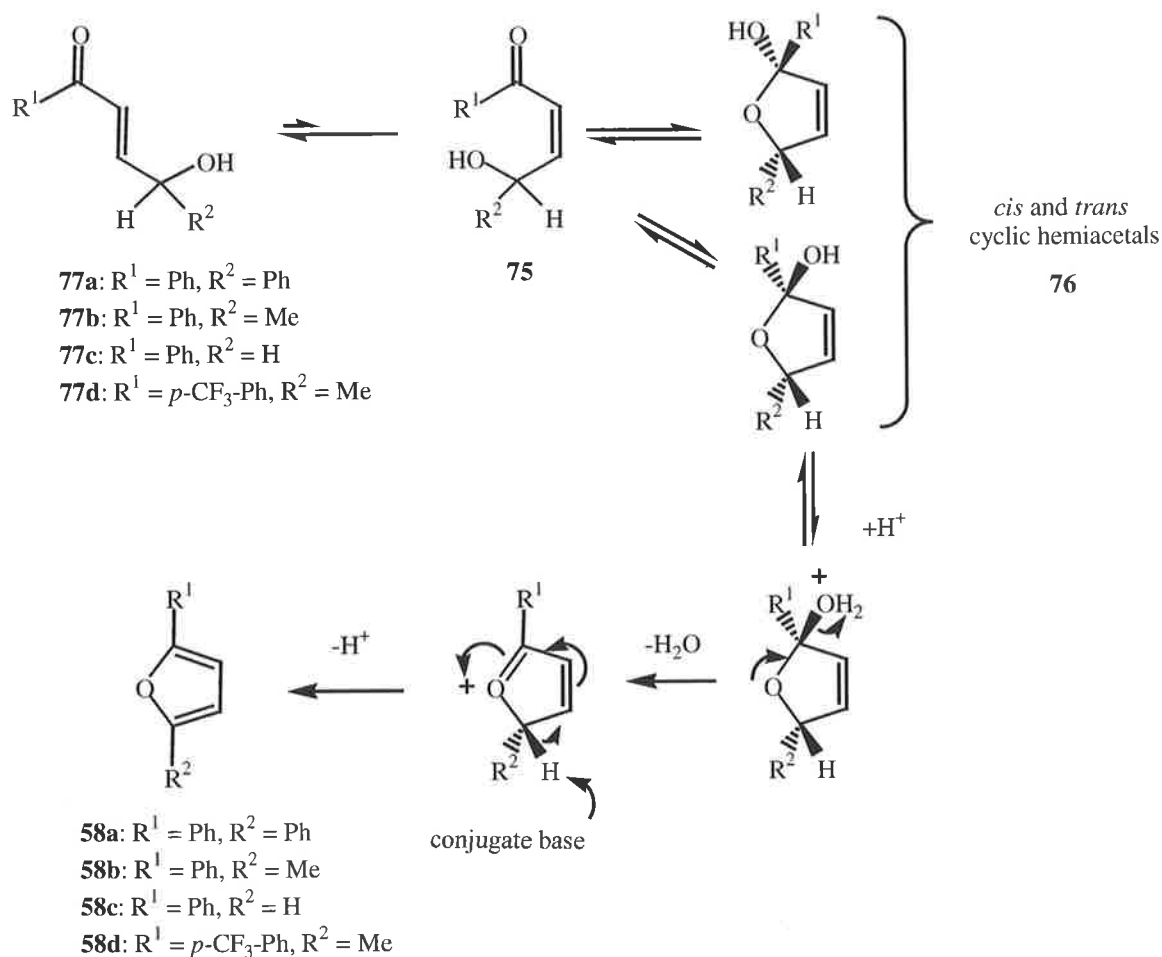
^a Refer to the Experimental Section for a general synthetic procedure.

This is consistent with the findings of Coxon *et al.*, Scheme 28, with furan arising presumably from rearrangement of the *trans* γ -hydroxy enones to their corresponding *cis* γ -hydroxy enones. Following this, cyclisation to yield hemiacetal and subsequent dehydration in the manner illustrated in Scheme 37 would lead to the generation of furan. Formation of furans from 1,2-dioxines of type (**56**) have previously been reported to proceed via metal catalysed rearrangement.^{104,105}

Acid catalysis of the furan formation was demonstrated by addition of *p*-TSA to *trans* γ -hydroxy enone (**77a**), which afforded furan (**58a**) in near quantitative yield.

Stabilisation of the *trans* γ -hydroxy enone was achieved by the addition of TPP to the samples, and when stored at 4 °C in CH_2Cl_2 the lifetime was increased considerably. It is proposed that TPP imparts stability to the *trans* γ -hydroxy enones by catalyzing the isomerisation of *cis* γ -hydroxy enones to *trans* γ -hydroxy enones.

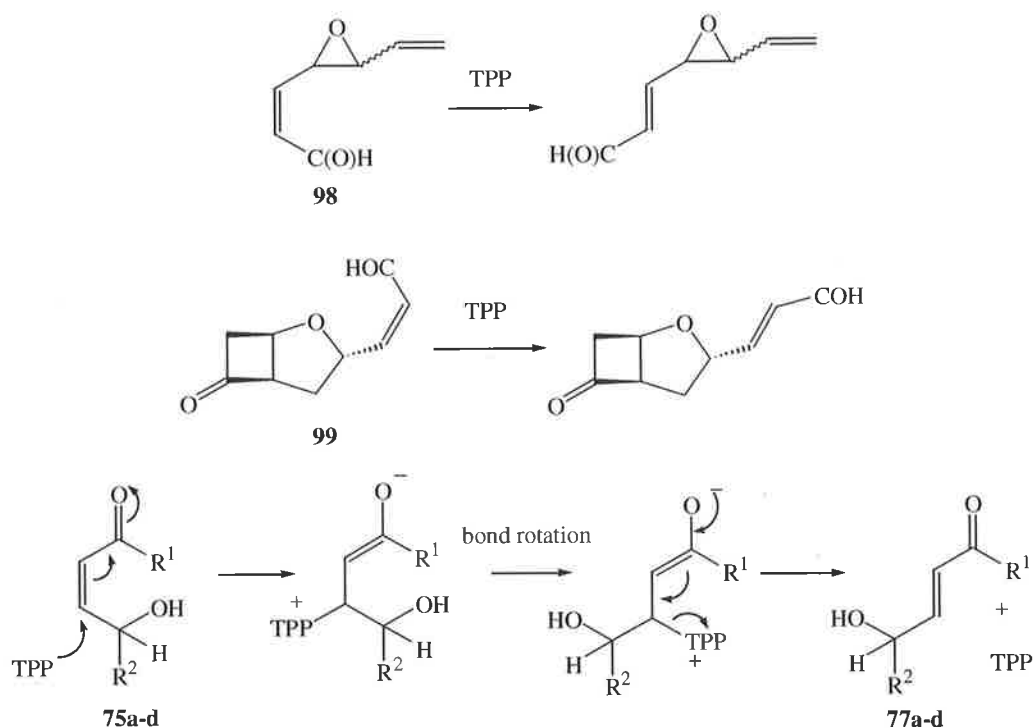
Scheme 37



TPP lowers the activation energy to isomerisation, allowing the reaction to operate under thermodynamic control, where the *trans* γ -hydroxy enone is the more stable isomer, Scheme 38. In this way, no significant build up of furan was observed in the presence of TPP by preventing the formation of *cis* γ -hydroxy enones.

Indeed TPP has been employed to effect *cis* to *trans* isomerisations of α,β -unsaturated aldehydes (**98**) and (**99**) with oxygen functionality at the γ position, Scheme 38.¹⁰⁶⁻¹⁰⁸ However, no mechanistic rationalisation was presented for these transformations.

Scheme 38



In these literature examples and for *trans* γ -hydroxy enones (**77a-d**), it was now proposed that reversible Michael addition of TPP to the *cis* olefin accounts for the isomerisation to the more thermodynamically stable *trans* olefin, Scheme 38.

Reaction of *trans* γ -hydroxy enones and stabilised ylides

With *trans* γ -hydroxy enones (**77a-d**) in hand an investigation of their involvement in the formation of cyclopropanes was conducted. *trans* γ -Hydroxy enones (**77a-d**) were allowed to react with stabilised phosphorus ylides (**55a,c-e**) in dichloromethane, this resulted in the formation of the desired cyclopropanes, as depicted in Scheme 39 and within Table 5.

A distinct discrepancy between the yields and reaction times of cyclopropane formation starting with *trans* γ -hydroxy enone as opposed to 1,2-dioxine became apparent with comparison of the results from Table 5 with those from Table 2. In general, all reactions took a considerably longer time to reach completion and in some cases, most noticeably

for *trans* γ -hydroxy enone (**77a**) the yield of cyclopropane was diminished in favor of 1,4-dicarbonyl (**59a**). From this evidence, it was concluded that the *trans* γ -hydroxy enones are not the key intermediates in the formation of cyclopropane.

Scheme 39

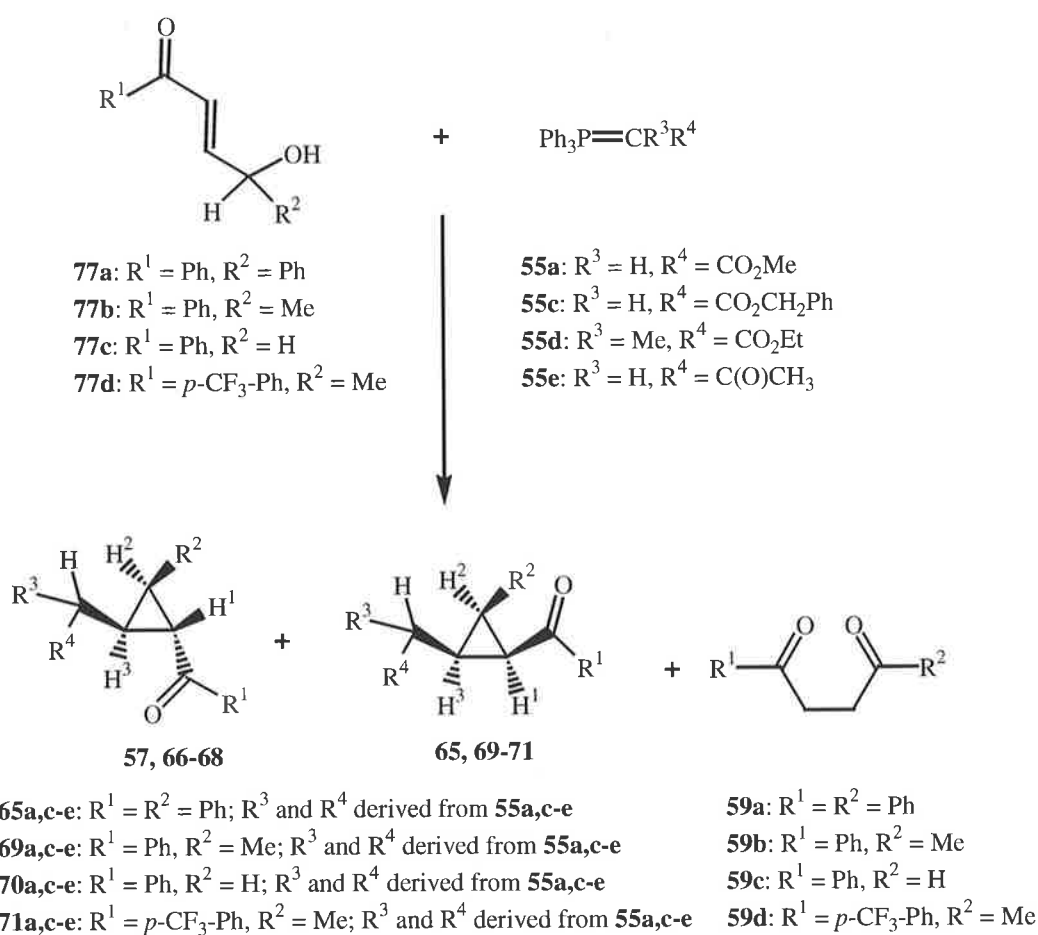


Table 5. Reaction of Stabilised Ylides 55a,c-e with *trans* γ -Hydroxy Enones 77a-d.^a

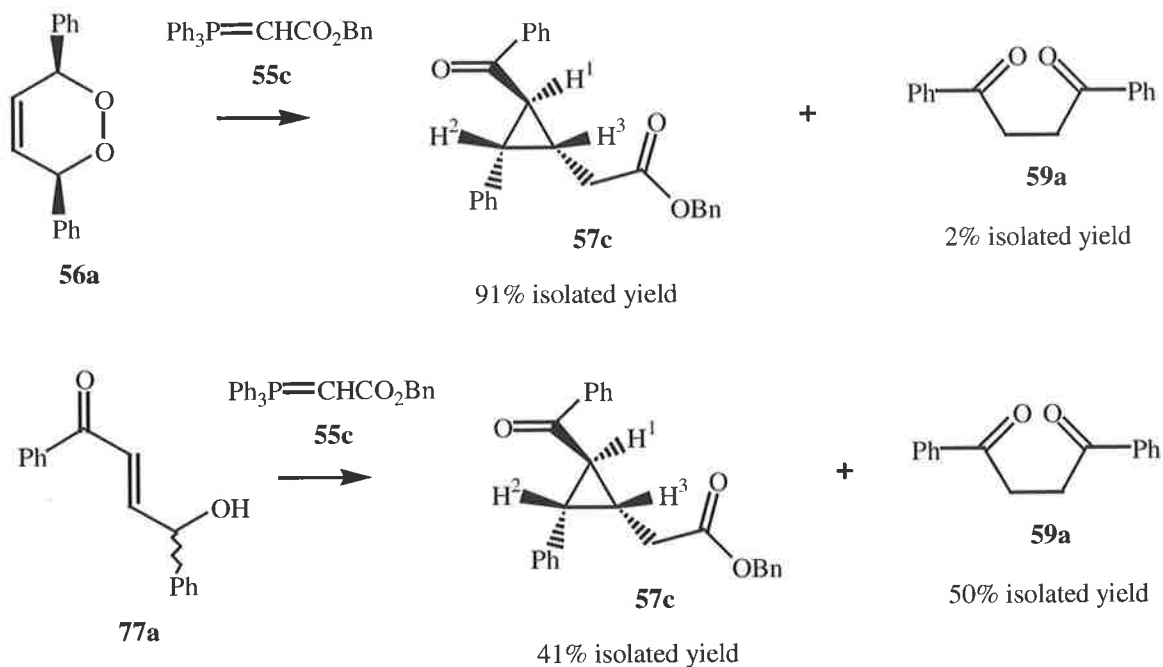
<i>trans</i> γ -hydroxy				
entry	enone	ylide	product(s); yield (%)	reaction time
1	77a	55c	57c ; (44), 59a ; (56)	2 weeks
2		55d	57d ; (5), 59a ; (95)	7 days
3		55e	59a ; (100)	4 days
4	77b	55c	66c ; (77), 69c ; (18), 59b ; (5)	4 weeks ^b
5		55e	59b ; (100)	2 weeks ^b
6	77c	55a	67a ; (100)	2 weeks ^b
7		55c	67c ; (100)	2 weeks
8	77d	55c	68c ; (78), 71c ; (15) ^c , 59d ; (7)	8 days

^a All reactions were performed in CH₂Cl₂ at ambient temperature; yields were determined from ¹H NMR (300 or 600 MHz) analysis of the crude reaction mixtures; isolated yields were within 10% of those reported. Refer to the Experimental Section for a general synthetic procedure. ^b 50% conversion of starting materials to products. ^c Characterised as α,β -unsaturated ester **72c**.

The discrepancy of yields is also unusual. In comparison of entry 3 of Table 2 and entry 1 of Table 5 an increase in the 1,4-dicarbonyl (**59a**) yield at the expense of cyclopropane to over 50% of the product ratio, was observed, Scheme 40. This result indicates that the *trans* γ -hydroxy enone is not the key intermediate in cyclopropanation, as identical or higher yields would be expected when starting with *trans* γ -hydroxy enones or 1,2-dioxines.

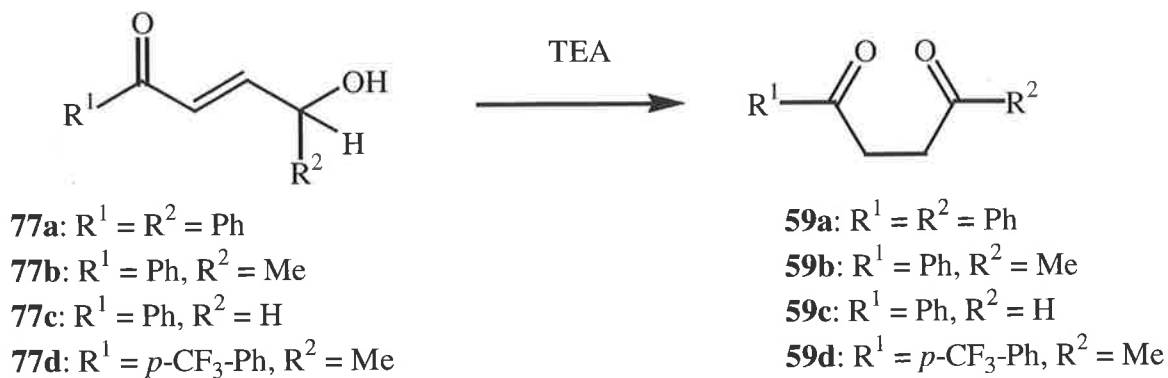
Even though the *trans* γ -hydroxy enone is not the key intermediate along the pathway to cyclopropane formation they do represent an alternate route by which to obtain cyclopropanes.

Scheme 40



Interest at this stage was concerned with why more of the 1,4-dicarbonyl formed when starting with *trans* γ -hydroxy enone as opposed to entry into the cyclopropane manifold from the 1,2-dioxines. In partial answer to the question, it was found that treatment of purified *trans* γ -hydroxy enones (**77a-d**) with base (10 equivalents of TEA) resulted in the quantitative conversion to the corresponding 1,4-dicarbonyl compounds (**59a-d**), Scheme 41.

Scheme 41



This parallels the formation of 1,4-dicarbonyls from 1,2-dioxines under identical conditions, discussed in Chapter 1, Scheme 23. Formation of 1,4-dicarbonyls in this way suggests that *trans* γ -hydroxy enones undergo the Kornblum-de la Mare rearrangement, Scheme 23. However, in order to undergo this reaction, the *trans* γ -hydroxy enones would have to rearrange to generate the isomeric *cis* γ -hydroxy enones necessary for this transformation. Evidence for this already existed with the observation that *trans* γ -hydroxy enones undergo acid catalysed rearrangement to their corresponding furans, which can only proceed through the intermediacy of the *cis* γ -hydroxy enone, Scheme 37. Also supporting the existence of *cis* γ -hydroxy enones, is the fact that TPP catalyses the *cis* – *trans* γ -hydroxy enone isomerisation, Scheme 38.

Although the intermediacy of the *cis* γ -hydroxy enone is proposed along the pathways to furan and 1,4-dicarbonyl formation, direct spectroscopic observation of this species had not been made. There was also no clear explanation for why 1,4-dicarbonyl formation increases in reactions from *trans* γ -hydroxy enones as opposed to 1,2-dioxines. Therefore, investigations into the formation of *cis* γ -hydroxy enones were initiated in order to understand the origins of 1,4-dicarbonyls and cyclopropanes.

Summary and Conclusion

Investigations in this chapter showed that the *trans* γ -hydroxy enones were not the key intermediates in the reaction of stabilised phosphorus ylides (**55**) and 1,2-dioxines (**56**). The time taken for cyclopropanation to occur starting from 1,2-dioxines ranges from 1 day to a week. In all cases starting with *trans* γ -hydroxy enone we see reaction times in the order of several weeks. This observation, coupled with the presence of higher proportions of 1,4-dicarbonyl in the reactions starting with *trans* γ -hydroxy enones, demonstrates that the *trans* γ -hydroxy enones are not the key intermediates along the pathway to cyclopropanes.

Research, however, did reveal a new route to cyclopropanes via *trans* γ -hydroxy enones. The method for *trans* γ -hydroxy enone synthesis elucidated within this chapter is high

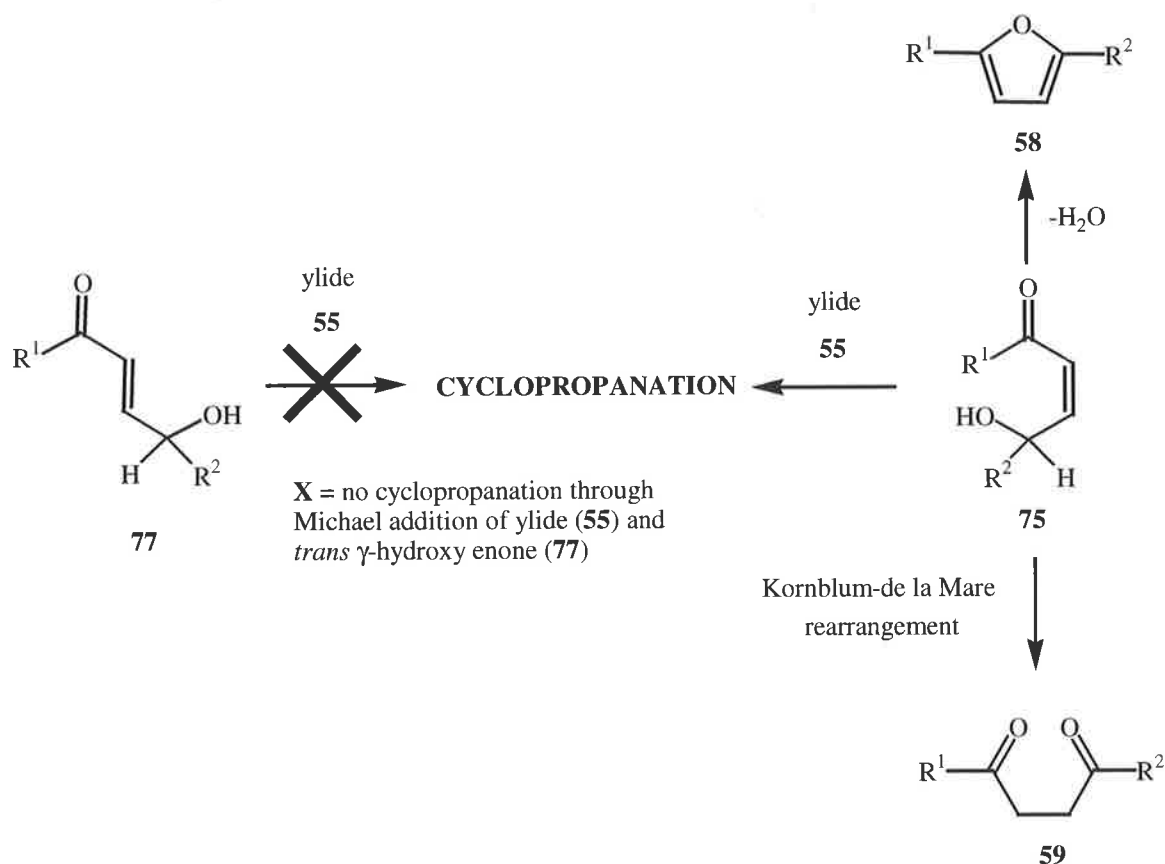
yielding and general for a range of 1,2-dioxines, thus, providing easy access to an underutilised synthon. Alternate synthesis of *trans* γ -hydroxy enones may and has led to the synthesis of cyclopropanes not accessible via the 1,2-dioxine route^{92,109} and as previously mentioned the synthesis of enantiomerically-pure cyclopropanes.⁹²

Chapter 3: *cis* γ -Hydroxy Enones

Introduction

In the previous chapter it was demonstrated that cyclopropanation did not proceed directly from the proposed *trans* γ -hydroxy enone intermediate. Alternatively it has been suggested that the isomeric *cis* γ -hydroxy enone could represent the key intermediate along the pathway to cyclopropane, Scheme 42.

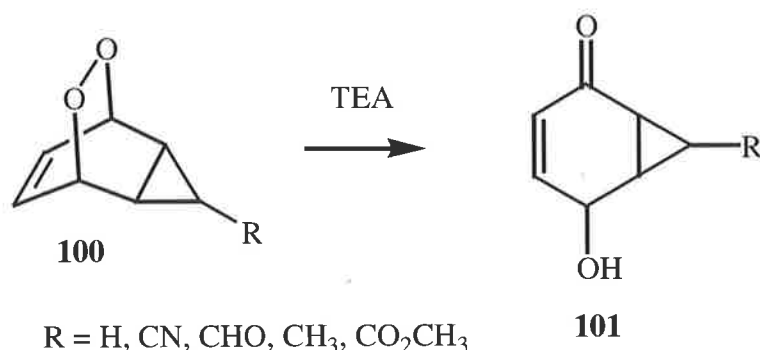
Scheme 42



Two classes of *cis* γ -hydroxy enones are evident from the literature, cyclic and acyclic. All examples of cyclic *cis* γ -hydroxy enones arise from either base induced^{110,111} or metal

catalysed decomposition of various bicyclic endoperoxides.^{102,112} A typical example of the metal catalysed transformation has been described in Chapter 2, Scheme 29 and 30. Base induced rearrangement simply involves the removal of the most acidic proton α to the oxygen-oxygen linkage and re-protonation of the alkoxide formed, Scheme 43.

Scheme 43

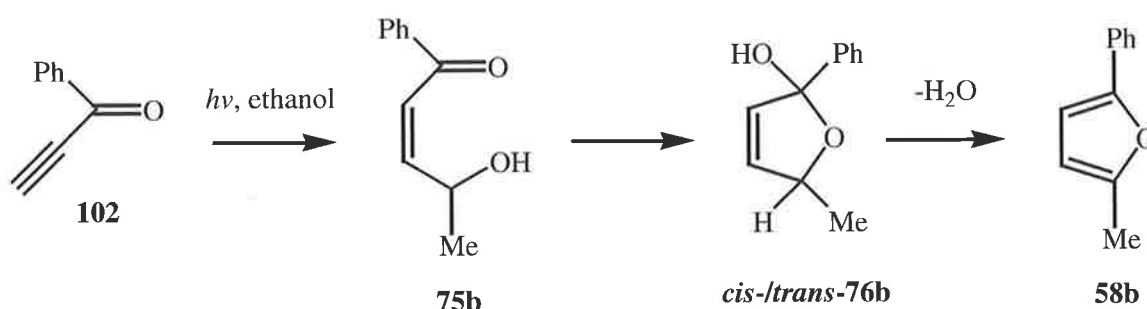


There are four literature methods detailing the construction of acyclic *cis* γ -hydroxy enones and/or corresponding *cis* / *trans* cyclic hemiacetals. These methods include; (i) the previously mentioned Stille coupling of organotin reagents with acid chlorides (Scheme 27 and associated text); (ii) the photochemical reactions of 1-phenyl-2-propyn-1-one in alcohols; (iii) the sodium borohydride reduction of α,β -unsaturated 1,4-diketones and (iv) metal catalyst promoted rearrangement of 1,2-dioxines.

Photochemical reactions of 1-phenyl-2-propyn-1-one

Photolysis of 1-phenyl-2-propyn-1-one (**102**) in alcohols such as methanol and ethanol are known to give rise to 2,5-substituted furans in yields of about 20-30%, Scheme 43.¹¹³ ¹H NMR analysis of the crude reaction mixture when 1-phenyl-2-propyn-1-one (**102**) and ethanol when placed under photolytic conditions revealed that a small proportion of the reaction mixture was represented by *cis* γ -hydroxy enone (**75b**). Although proposed in the rearrangement to furan (**58b**), the presence of cyclic hemiacetals (*cis*-/*trans*-**76b**) was not observed.

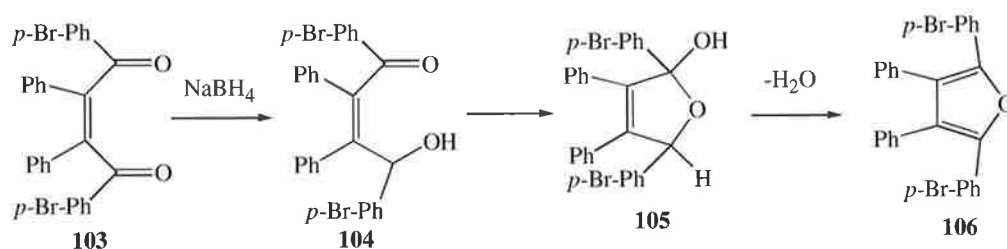
Scheme 44



Sodium borohydride reduction of α,β -unsaturated 1,4-diketones

The reduction of α,β -unsaturated 1,4-diketones by sodium borohydride has been used to create 2-hydroxy-2,5-dihydrofurans more commonly referred to within this thesis as cyclic hemiacetals.^{114,115} A report by Freedman *et al.* describes the reaction of diketone (**103**) with sodium borohydride.¹¹⁵ This reaction yielded 2-hydroxy-2,5-dihydrofuran (**105**) in 85% isolated yield, Scheme 45. Although not detected, it was proposed that formation of (**105**) proceeded via the intermediate *cis* γ -hydroxy enone (**104**). As expected, rapid rearrangement ensued upon treatment of (**105**) with acid to quantitatively yield furan (**106**).

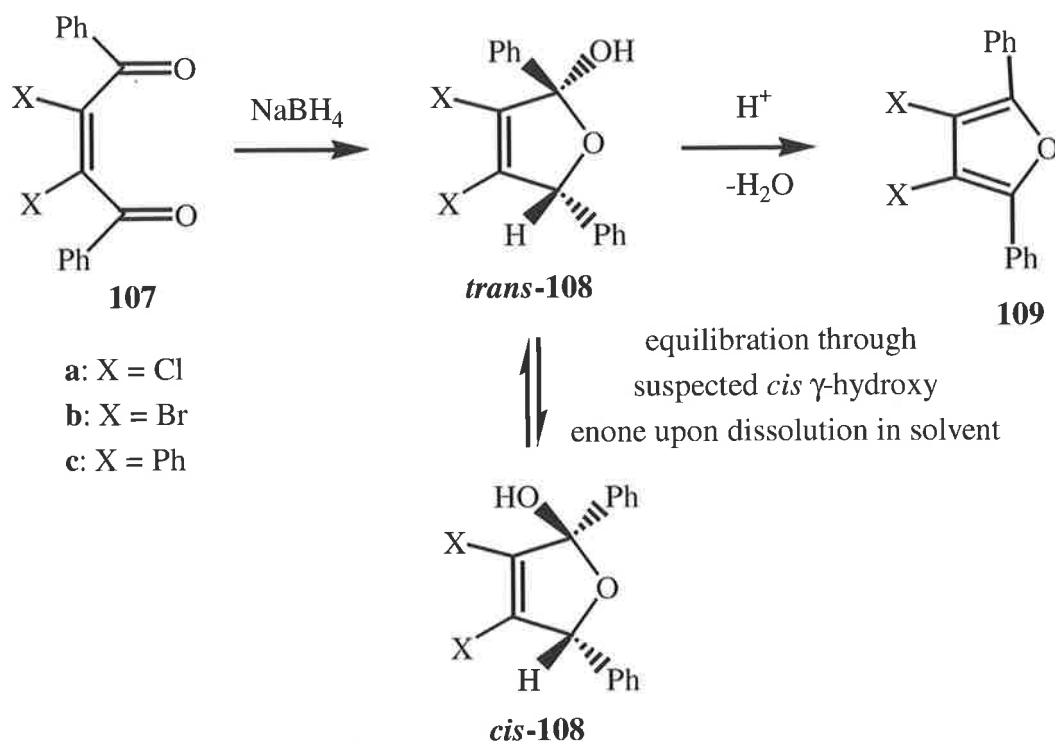
Scheme 45



The identical reaction was reported by Hankins *et al.* on diketones (**107a-c**), extensive characterisation was carried out on the resulting 2-hydroxy-2,5-dihydrofurans (**108a-c**).¹¹⁴ It was determined by various spectroscopic techniques that all 2-hydroxy-2,5-dihydrofurans were present in their *trans* form. Upon dissolution in CDCl_3 , equilibration

of the *trans* 2-hydroxy-2,5-dihydrofurans (***trans*-108a-c**) with the *cis* (***cis*-108a-c**) anomer was observed in all cases, Scheme 46. Formation of the *cis* anomer was proposed to proceed through a corresponding *cis* γ -hydroxy enone intermediate, however, none were spectroscopically observed or detected. Dissolution of the *trans* 2-hydroxy-2,5-dihydrofurans (***trans*-108a-c**) also resulted in slow decomposition to the corresponding furans (**109**) via dehydration.

Scheme 46

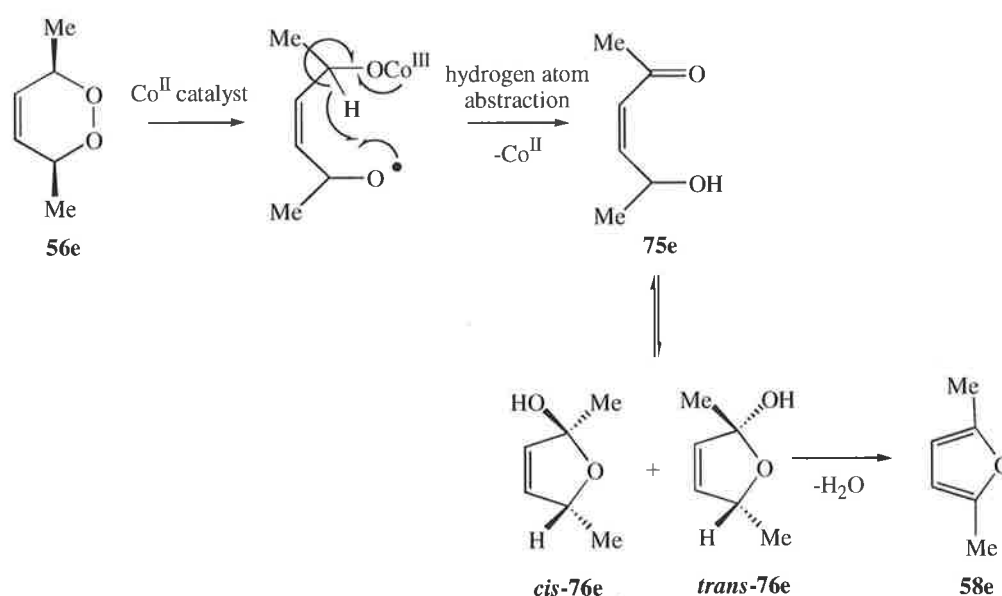


Decomposition of endoperoxides

As highlighted previously, endoperoxides are known to give rise to cyclic *cis* γ -hydroxy enones upon treatment with base, Scheme 23, or transition metal catalyst such as $\text{Pd}(\text{PPh}_3)_4$, Scheme 29. Although there are many examples in the literature, there is only one paper detailing the formation of an acyclic *cis* γ -hydroxy enone and its corresponding *cis* and *trans* cyclic hemiacetals via the metal catalysed rearrangement of endoperoxides.¹⁰⁴

Catalysts CoTPP or Co(SALEN)₂ were utilised to effect the transformation of 1,2-dioxine (**56e**) into its corresponding *cis* γ -hydroxy enone (**75e**) and hemiacetals (*cis*-/*trans*-**76e**), which were characterised through extensive two dimensional NMR techniques. The rearrangement of the 1,2-dioxine (**56e**) occurred over several hours at ambient temperature in the presence of 5-10% catalyst. Decomposition of the resultant equilibrium mixture of *cis* γ -hydroxy enone and hemiacetals gave quantitative formation of 2,5-dimethylfuran (**58e**), Scheme 47.

Scheme 47



The reaction is thought to be initiated by catalytic cleavage of the peroxide bond in an electron transfer process. This is followed by a hydrogen atom abstraction process, with regeneration of the cobalt catalyst. Formation of the furan proceeded via dehydration as discussed in earlier examples, Scheme 37.

It was also reported¹⁰⁴ that treatment of the 1,2-dioxine (**56a**) with cobalt catalyst in the identical manner to (**56e**) also led to the expeditious formation of 2,5-diphenylfuran (**58a**). However, the presence of the corresponding *cis* γ -hydroxy enone (**75a**) or cyclic hemiacetals (*cis*-/*trans*-**76a**) was not spectroscopically observed.

Two other examples of similar reactions of endoperoxides yielding acyclic *cis* γ -hydroxy α,β -unsaturated aldehydes and their corresponding hemiacetals also exist, completely corroborating the base and metal catalysed mechanisms discussed in the previous examples.^{116,117} These acyclic *cis* γ -hydroxy α,β -unsaturated aldehydes are also known to undergo acid or metal catalysed rearrangement to their corresponding furans.^{116,117}

Once again a general method was required for the synthesis of the desired *cis* γ -hydroxy enones instead of individual routes. Thus, the approaches concerned with the base and metal catalysed rearrangements of 1,2-dioxines were selected for investigations into the synthesis of *cis* γ -hydroxy enones.

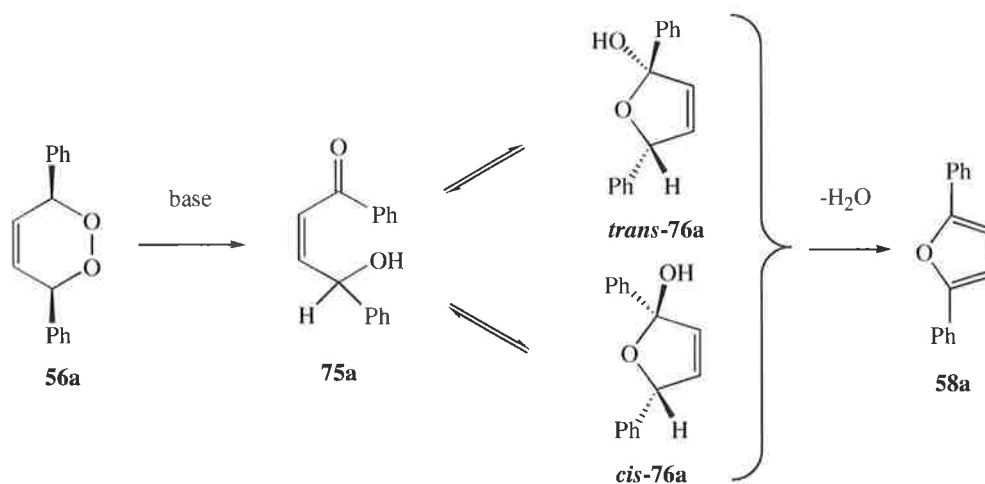
Results and Discussion

Base catalysed synthesis of *cis* γ -hydroxy enones

cis γ -Hydroxy enones and their corresponding *cis* / *trans* cyclic hemiacetals have previously been proposed as intermediates along the pathway to 1,4-dicarbonyl formation, Scheme 23.⁹⁰ Therefore, an experiment was set up to monitor the interaction of 1,2-dioxine **56a** with 1 equivalent of TEA, in the absence of TPP, by ¹H NMR. Several intermediates were observed along the pathway to 1,4-dicarbonyl (**59a**) (approximately 10% of the reaction mixture at any one time). An attempt was then made to isolate the intermediates via column chromatography. ¹H NMR analysis of the three fractions collected from the column showed identical ratios of three compounds in each.

It was, therefore, suspected that the intermediates were the *cis* γ -hydroxy enone (**75a**) in equilibrium with its *cis* / *trans* cyclic hemiacetals (*cis*-/*trans*-**76a**), Scheme 48.

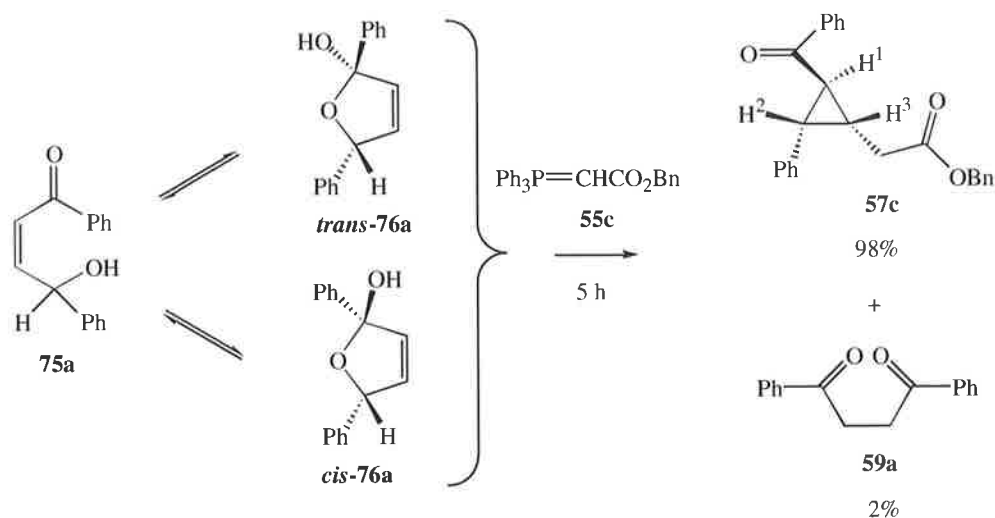
Scheme 48



Treatment of the mixture with D₂O showed exchange of three protons in the ¹H NMR spectrum (two singlets at δ 2.95 and δ 3.04 and a doublet at δ 3.68 ppm, indicating three products all containing OH functionality. Over time these three compounds rearranged to generate furan (**58a**). The formation of the furan suggested that the intermediates isolated were the desired *cis* γ -hydroxy enone (**75a**) and its *cis* / *trans* cyclic hemiacetals (*cis*-/*trans*-**76a**).

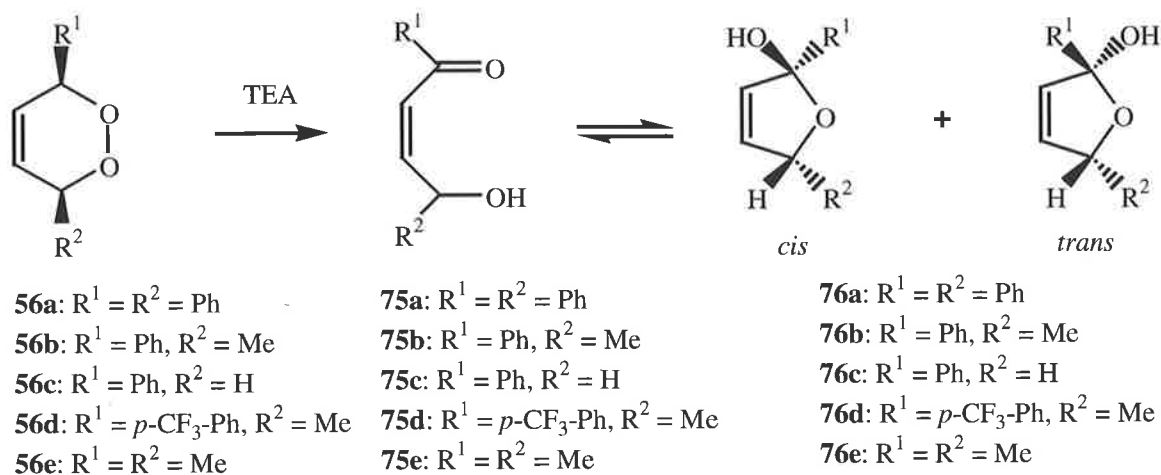
Addition of ylide (**55c**) to the mixture of *cis* γ -hydroxy enone (**75a**) and cyclic hemiacetals (*cis*-/*trans*-**76a**), and monitoring by ¹H NMR showed formation of cyclopropane (**57c**) in near quantitative yield over five hours, Scheme 49. The conversion of *cis* γ -hydroxy enone (**75a**) and cyclic hemiacetals (*cis*-/*trans*-**76a**) into cyclopropane in such a rapid time frame and high yield, indicates that either the *cis* γ -hydroxy enone (**75a**) or the cyclic hemiacetals (*cis*-/*trans*-**76a**) are the intermediates through which cyclopropane formation proceeds.

Scheme 49



Continuing with this method, the TEA (1 equivalent) catalysed rearrangement of 1,2-dioxines (**56a-e**) was utilised to synthesise a range of *cis* γ -hydroxy enones (**75a-e**) and their cyclic hemiacetals (*cis*-/*trans*-**76a-e**), Scheme 50.

Scheme 50



Accurate yield determination proved difficult due to the delicate balance between maximising the formation of *cis* γ -hydroxy enone (**75**) and minimising the competing reactions leading to the formation of *trans* γ -hydroxy enone (**77**), furan (**58**) and 1,4-

dicarbonyl (**59**) products. *cis* γ -Hydroxy enone (**75a-e**) formation was maximised with close monitoring by TLC. Subsequent column chromatography yielded *cis* γ -hydroxy enone and hemiacetals in approximately 30% isolated yield in all cases. A good portion of the products was lost during column chromatography as the *cis* γ -hydroxy enones (**75a-e**) and its hemiacetals (*cis*-/*trans*-**76a-e**) rearrange, forming furans (**58a-e**) on exposure to silica gel. The substitution of alumina as solid support for the column gave a comparable amount of breakdown. Consequently, only the synthesis of small amounts was possible at any one time, approximately 50–100 mg. This procedure, however, enabled the characterisation of the *cis* γ -hydroxy enones (**75a-e**) and necessary experimentation.

The *cis* γ -hydroxy enones (**75a-e**) and cyclic hemiacetals (*cis*-/*trans*-**76a-e**) once isolated were found to rapidly rearrange into their corresponding furans (**58a-e**), in the order of hours. The decomposition time was extended marginally, to the order of 2 days, by storage at low temperature (-15 °C), however, in order to avoid furan formation the *cis* γ -hydroxy enones were always utilised immediately.

It was also demonstrated that *cis* γ -hydroxy enones (**75a-e**) and their corresponding cyclic hemiacetals (*cis*-/*trans*-**76a-e**) undergo base catalysed rearrangement to 1,4-dicarbonyl. This was shown by the treatment of the mixture (**75a**) and (*cis*-/*trans*-**76a**) with TEA (10 equiv.) in dichloromethane, resulting in the quantitative formation of 1,4-dicarbonyl (**59a**). This experiment confirms that the formation of 1,4-dicarbonyl proceeds through the intermediacy of *cis* γ -hydroxy enones and their cyclic hemiacetals as proposed in Chapter 1, Scheme 23.

The ratio of *cis* γ -hydroxy enones (**75a-e**) and their cyclic hemiacetals (*cis*-/*trans*-**76a**) were determined initially (Table 6), however, the instability of these mixtures made characterisation of the compounds difficult.

Table 6. Ratio of *cis* γ -Hydroxy Enones **75a-e to *cis* / *trans* Hemiacetals **76a-e** in CDCl₃.^a**

entry	1,2-dioxine	<i>cis</i> γ -hydroxy enone : <i>cis</i> / <i>trans</i> hemiacetal ratio (%) ^b
1	53a	75a (67) : 76a (33)
2	53b	75b (79) : 76b (21)
3	53c	75c (100) : 76c (0)
4	53d	75d (29) : 76d (71)
5	53e	75f (18) : 76f (82)

^a All ratios were determined in CDCl₃ (600 MHz, ¹H NMR) at ambient temperature with identical volumes and concentrations. ^b Ratio estimated by comparison of OH peak integration from ¹H NMR spectra.

Only minimal characterisation of (**75a-e**) was obtained as instability prevented extensive analysis. The presence of the two hemiacetals (*cis*-/*trans*-**76a**) also made difficult the characterisation. Hemiacetal characterisation was not possible for these reasons and also due to signal overlap in the ¹H NMR spectra. *cis* γ -Hydroxy enone (**75c**) was more extensively characterised as there was negligible hemiacetal present. Spectral data for (**75e**) and (*cis*-/*trans*-**76e**) were identical to those quoted by Foote *et al.*¹⁰⁴

Metal catalysed synthesis of *cis* γ -hydroxy enones

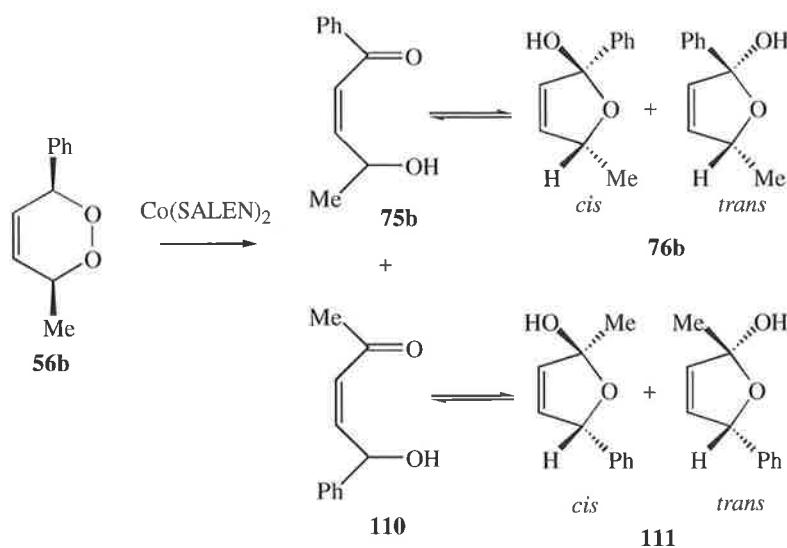
Although the technique described above enabled the synthesis of the *cis* γ -hydroxy enones (**75a-e**) and their cyclic hemiacetals (*cis*-/*trans*-**76a**), the poor yields and micro-scale syntheses prompted investigations into the metal catalysed rearrangement of 1,2-dioxines (**56a-e**).

Previous synthesis of *cis* γ -hydroxy enone (**75a**) and (*cis*-/*trans*-**76a**) demonstrated that it was possible to synthesise and isolate (**75a**) and (*cis*-/*trans*-**76a**). For this reason repetition of the reaction by Foote *et al.*¹⁰⁴ using Co(SALEN)₂ catalyst (2 mol%) was performed. Quantitative conversion of 1,2-dioxine (**56a**) into *cis* γ -hydroxy enone (**75a**) and hemiacetals (*cis*-/*trans*-**76a**) was observed by ¹H NMR after a reaction time of five hours in CDCl₃. It is unsure as to why this reaction was successful in this case, in light of the failure of Foote *et al.* to obtain (**75a**) and (*cis*-/*trans*-**76a**). The presence of water could be ruled out as a contributing factor due to the equally reactive nature of

Co(SALEN)₂ hexahydrate under these reaction conditions. Successful repetition of the Co(SALEN)₂ (2 mol%) catalysed rearrangement of 1,2-dioxine (**56e**) proceeded as described in the paper by Foote *et al* to give quantitative formation of *cis* γ -hydroxy enone (**75e**) and hemiacetals (*cis*-/*trans*-**76e**).¹⁰⁴

The Co(SALEN)₂ catalysis, as expected did not translate well to the rearrangement of unsymmetrical 1,2-dioxines (**56b-d**). Unlike the base catalysed rearrangement of 1,2-dioxines, the Co(SALEN)₂ catalysed reactions are not regioselective in nature. Consequently, treatment of 1,2-dioxine (**56b**) with Co(SALEN)₂ (2 mol.%) led to a mixture of *cis* γ -hydroxy enone regioisomers (**75b**) and (**110**) and their corresponding hemiacetals (*cis*-/*trans*-**76b**) and (*cis*-/*trans*-**111**), Scheme 51. This procedure was, therefore, unsuitable for use in the rearrangement of unsymmetrical 1,2-dioxines (**56b-d**) and subsequent cyclopropanation. Cobalt catalysis, however, enabled much larger quantities of *cis* γ -hydroxy enone (**75a**) and (**75e**) to be synthesised in near quantitative yields.

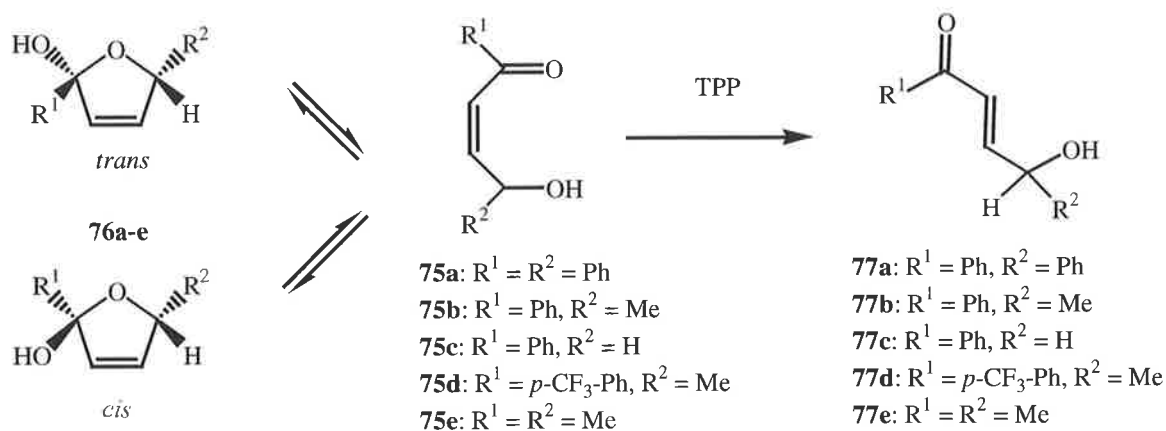
Scheme 51



Decomposition of the *cis* γ -hydroxy enones (**75a,e**) formed via cobalt catalysis is restricted to rearrangement and dehydration to form furans (**58a,e**). Formation of *trans* γ -hydroxy enone (**77a,e**) and 1,4-dicarbonyl (**59a,e**) products are avoided due to the neutral nature of the reaction and a lack of “free” nucleophiles in solution (eg TEA, TPP).

Synthesis of the *trans* γ -hydroxy enones (**77a-e**) from the *cis* γ -hydroxy enones (**75a-e**) is possible utilising the technique described in Chapter 2. Treatment of all *cis* γ -hydroxy enones (**75a-e**) with 0.5 equivalents of TPP resulted in the near quantitative formation of the *trans* γ -hydroxy enones (**77a-e**), Scheme 52.

Scheme 52

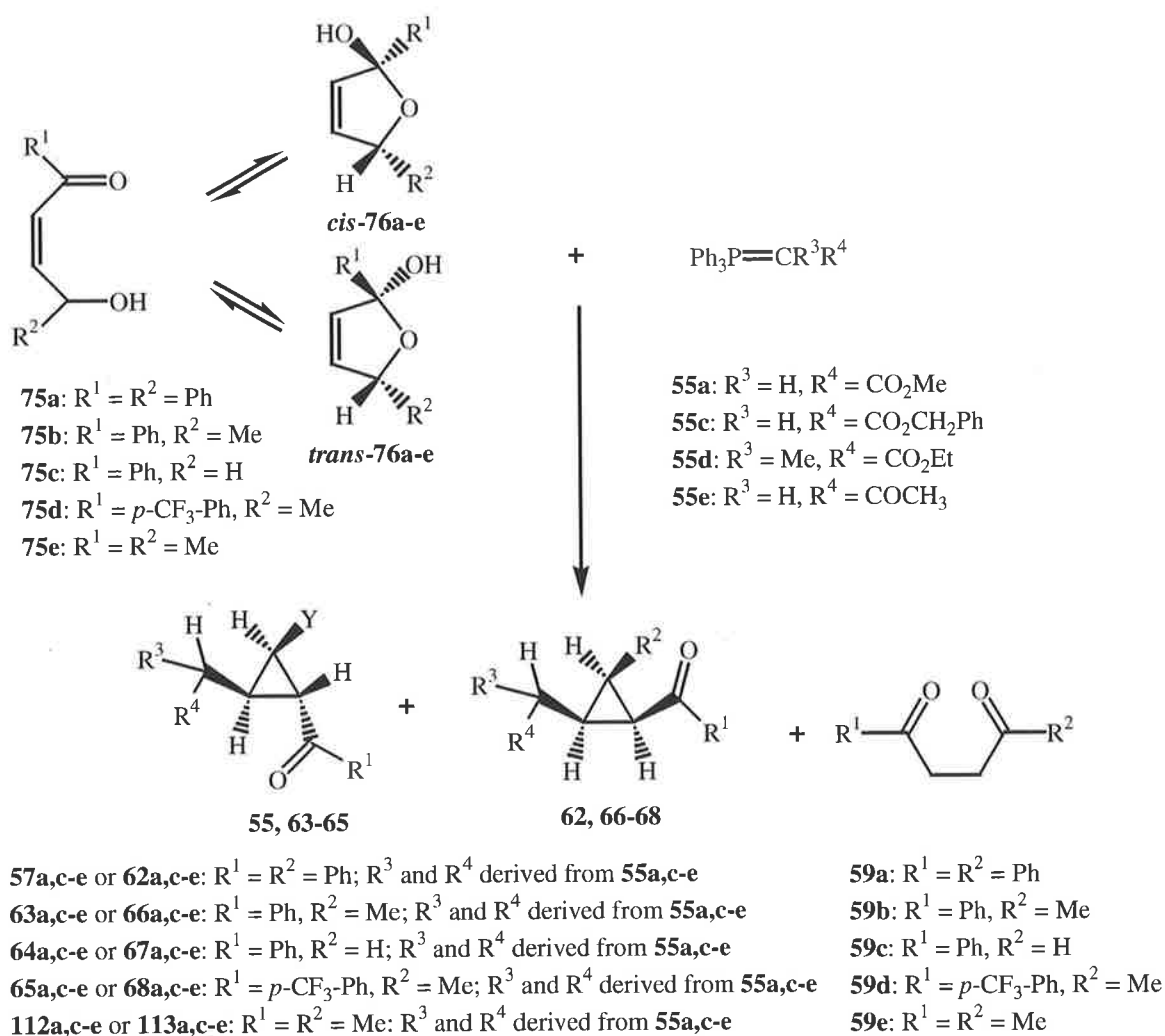


This confirms the hypothesis that the *trans* γ -hydroxy enones are stabilised by the action of TPP on the equilibrium of *cis* and *trans* γ -hydroxy enones. Therefore, if TPP is used in conjunction with the cobalt catalysed synthesis of *cis* γ -hydroxy enones (**75a,e**) then we have another highly efficient synthesis of *trans* γ -hydroxy enones (**77a,e**) from symmetrical 1,2-dioxines (**56a,e**).

Reaction of *cis* γ -hydroxy enones and stabilised ylides

In order to establish that the thermodynamic mixture of the *cis* γ -hydroxy enones (**75a-e**) and their cyclic hemiacetals (*cis*-/*trans*-**76a-e**) are the key intermediates along the reaction pathway to cyclopropane formation, all mixtures were allowed to react with a variety of stabilised phosphorus ylides (**55a,c-e**), Table 7.

Scheme 53



In all cases, the formation of cyclopropane from the *cis* γ -hydroxy enones (**75a-e**), proceeded in a more rapid time frame and in a yield equal to or better than that of cyclopropanes generated from the corresponding 1,2-dioxines (**56a-e**), Table 2. The ratios of the cyclopropyl diastereomers arising from reactions of *cis* γ -hydroxy enones (**75b**) and (**75d**) are also identical to the ratios generated from the initial 1,2-dioxines (**56b**) and (**56d**) respectively, Table 2. All evidence at this stage suggested that isomerisation of the 1,2-dioxine to the *cis* γ -hydroxy enone, cyclic *cis* / *trans* hemiacetal thermodynamic mixture was essential in the formation of cyclopropane. Furthermore, it can be concluded that cyclopropanation proceeds through Michael addition of the *cis* γ -hydroxy enone and ylide and not the cyclic hemiacetals and ylide, as *cis* γ -hydroxy enone

(**75c**) existed only in its uncyclised state. Further evidence to support this came from monitoring the reaction of 1,2-dioxine with Jacobsen's catalyst by ^1H NMR, as discussed in Chapter 6. this revealed that *cis* γ -hydroxy enone is generated quantitatively within 30 seconds and that equilibration with its *cis*/*trans* cyclic hemiacetals requires 5 minutes.

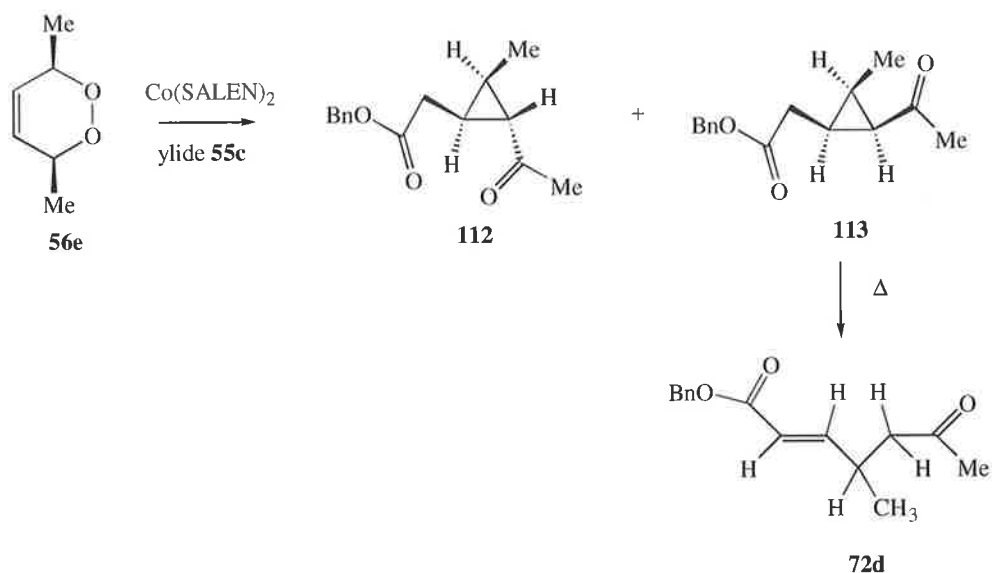
Table 7. Reaction of *cis* γ -Hydroxy Enones (75a-e**) / Hemiacetals (*cis*-/*trans*-**76a-e**) with Ylides (**55a,c-e**).^a**

entry	enone	ylide	reaction time (h)	product(s); yield (%)
1	75a ^c	55c	5	57c ; (98), 59a ; (2)
2		55d	4	57d ; (41), 59a ; (52) ^b
3		55e	4	59a ; (100)
4	75b ^d	55a	6	66a ; (82), 69a ; (18)
5		55c	6	66c ; (84), 69c ; (16)
6	75c ^d	55a	4	67a ; (100)
7		55c	4	67c ; (100)
8	75d ^d	55c	4	68c ; (82), 71c ; (18)
9	75e ^c	55c	72	112 ; (84), 113 ; (16)

^a All reactions performed in CDCl_3 at ambient temperature unless otherwise stated. Yields were determined from ^1H NMR spectra (300 or 600 MHz) of the crude reaction mixtures; isolated yields were typically within 10% of those reported. Refer to Experimental Section for a general synthetic procedure. ^b A small amount (7%) of another cyclopropyl isomer was detected and tentatively assigned as ethyl 1-methyl-2-(2-oxo-2-phenylethyl)-3-phenyl-1-cyclopropanecarboxylate (**73**) (Figure 12). ^c *cis* γ -hydroxy enones were generated by $\text{Co}(\text{SALEN})_2$ catalysed rearrangement and utilised without further purification. ^d *cis* γ -Hydroxy enones were generated via triethylamine catalysed rearrangement.

The successful synthesis of cyclopropanes from *cis* γ -hydroxy enone (**75e**) represents an increase in the scope of the cyclopropanation reaction, expanding the reaction to encompass dialkyl substituted 1,2-dioxines. $\text{Co}(\text{SALEN})_2$ catalyst plays an important role in the formation of cyclopropane from dialkyl substituted 1,2-dioxines as there was no cyclopropane formation when 1,2-dioxine (**56e**) and ylide (**55c**) were allowed to react, Scheme 54. The reason for this is that the ylide is not of sufficient basicity to effect rearrangement of the 1,2-dioxine (**56e**) to the *cis* γ -hydroxy enone (**75e**) via removal of the proton α to the oxygen-oxygen linkage.

Scheme 54



The two cyclopropyl isomers (**112**) and (**113**) formed in this reaction were of identical stereochemical structure to the cyclopropanes formed from the reaction of *trans* γ -hydroxy enones (**77a-d**) and ylides (**55**). Heating (**113**) at 60 °C for one day resulted in quantitative formation of α,β -unsaturated ester (**72d**) via an enolene rearrangement (refer to Scheme 21 for mechanism).

Summary and Conclusion

Investigations discussed within this chapter showed that the *cis* γ -hydroxy enones are the key intermediates necessary for cyclopropane formation from stabilised phosphorus ylides and 1,2-dioxines. The comparable ratios of cyclopropane isomers and 1,4-dicarbonyl formed within the reactions originating with 1,2-dioxines and *cis* γ -hydroxy enones coupled with the more rapid formation when starting with *cis* γ -hydroxy enones suggests that the *cis* γ -hydroxy enones are intermediates in cyclopropanation.

In addition, two methods for the synthesis of *cis* γ -hydroxy enones utilising either cobalt or base catalysed rearrangement have been expanded upon. Large-scale application is,

however, limited to the symmetrical 1,2-dioxines utilising the cobalt catalysed rearrangement.

During the investigation another route for the synthesis of *trans* γ -hydroxy enones (**77a-e**) was uncovered through the TPP catalysed rearrangement of *cis* γ -hydroxy enones (**75a-e**). This allows for the large-scale synthesis of *trans* γ -hydroxy enones (**77a,e**) from the symmetrical 1,2-dioxines (**56a,e**) via cobalt catalysis in near quantitative yield.

Treatment of *cis* γ -hydroxy enones (**75a-e**) and cyclic hemiacetals (*cis-trans*-**76a-e**) with TEA (10 equiv.) confirmed their intermediacy in the formation of 1,4-dicarbonyls (**59a-e**). This finding did not, however, reveal the reason behind the excessive 1,4-dicarbonyl formation when cyclopropanation was attempted using *trans* γ -hydroxy enones.

Chapter 4: Reaction Manifold and Mechanism

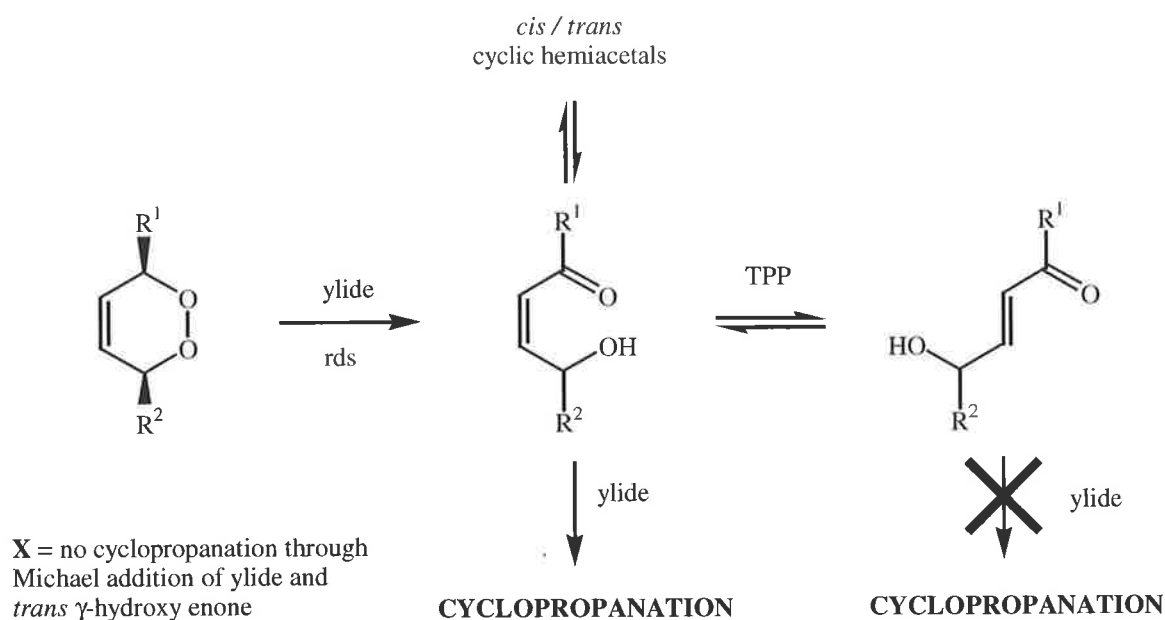
Introduction

Given the strong evidence for the intermediacy of *cis* γ -hydroxy enones (**75a-e**) along the pathway to cyclopropane formation from 1,2-dioxines (**56a-e**) and stabilised phosphorus ylides (**55**), the foundation has been laid for in-depth discussions addressing the two final mechanistic questions. Firstly the question of how and where the 1,4-dicarbonyl byproduct is arising when starting with *trans* γ -hydroxy enones and secondly, the mechanism of cyclopropane formation from the *cis* γ -hydroxy enones.

Results and Discussion

To begin with, the overall mechanistic picture as it stands needs to be considered, Scheme 55. Firstly, the ylide reacts as a base removing the most acidic proton α to the oxygen-oxygen linkage of the 1,2-dioxine. This step is the rate-determining step as has been demonstrated by the fact that the *cis* γ -hydroxy enones react with ylides more rapidly to form cyclopropanes than the 1,2-dioxines do with ylide. Rearrangement then yields the *cis* γ -hydroxy enone, which exists in equilibrium with its cyclic hemiacetals. The *cis* γ -hydroxy enones then react with ylides to form cyclopropanes.

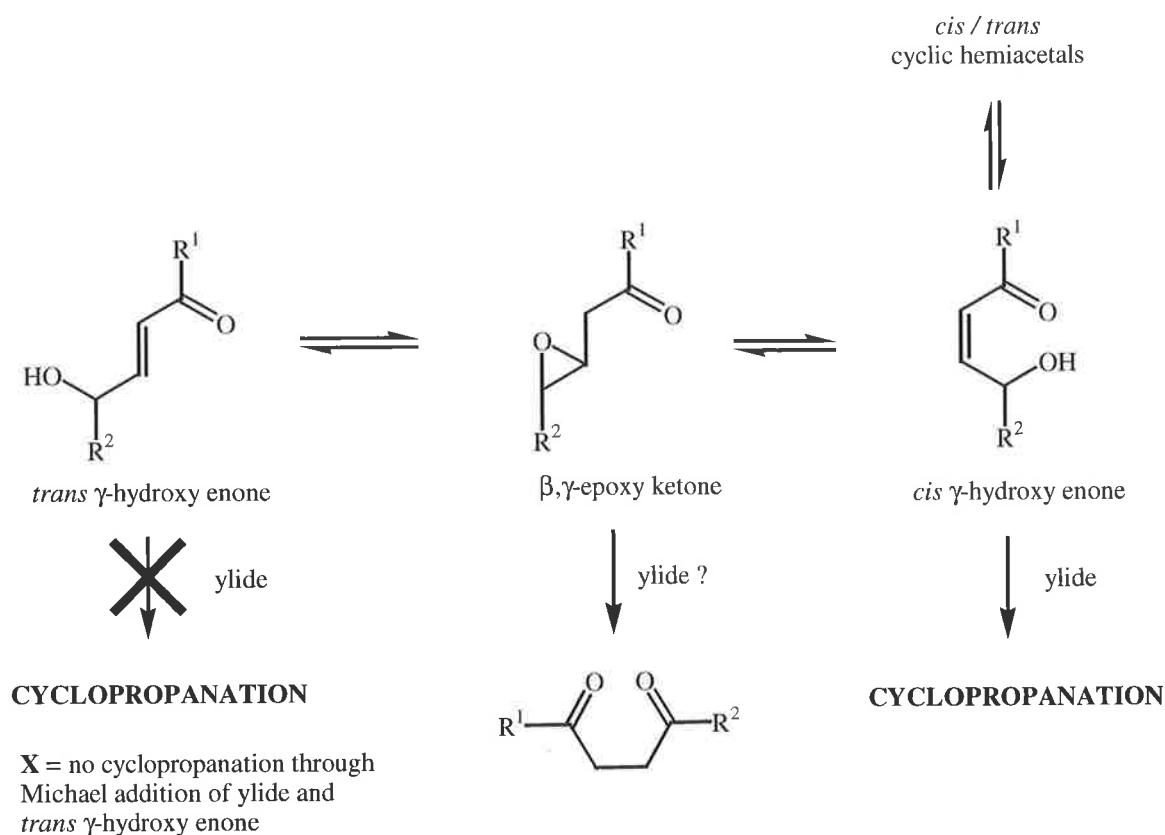
Scheme 55



It is also known that the *cis* γ -hydroxy enones can be converted into the corresponding *trans* γ -hydroxy enones through manipulation of the equilibrium between them, Scheme 52. Further evidence for the existence of an equilibrium was the observation, by ^1H NMR, of a small proportion of the *cis* γ -hydroxy enone (**75d**) within a purified sample of *trans* γ -hydroxy enone (**77d**) (approximately 5% of the sample). Therefore, in order to form cyclopropane utilising *trans* γ -hydroxy enones as a starting material, isomerisation to the *cis* γ -hydroxy enone is essential.

In the absence of TPP the *cis* / *trans* γ -hydroxy enone isomerisation may proceed through the intermediacy of a β,γ -epoxy ketone. This β,γ -epoxy ketone intermediate may in some manner contribute to the excess 1,4-dicarbonyl formation arising when cyclopropanation is attempted using *trans* γ -hydroxy enones, Scheme 56.

Scheme 56



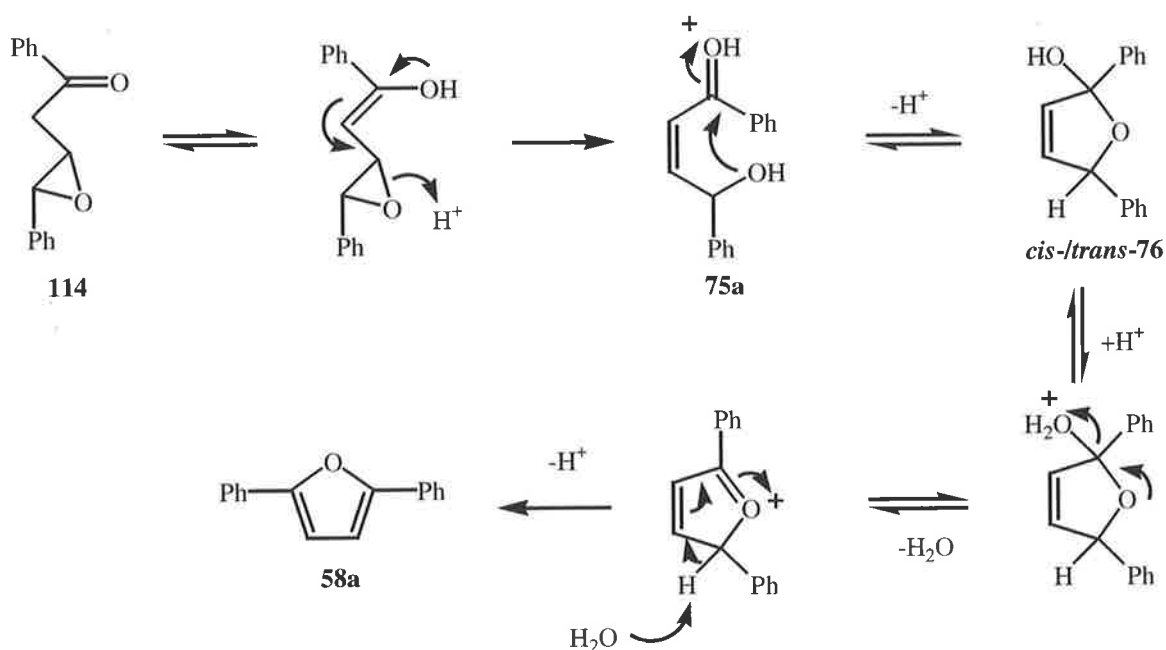
Although it is mechanistically difficult to see how such a process would occur it was envisaged that the preparation of β,γ -epoxy ketone (**114**), where $R^1 = R^2 = \text{Ph}$, would demonstrate its involvement (if any) in the formation of cyclopropanes from 1,2-dioxines and ylides.

β,γ -epoxy ketones

The decomposition of β,γ -epoxy ketones has been reported on two separate occasions.^{101,118} In Chapter 2 it was discussed how epoxide (**91**) led to the formation of *trans* γ -hydroxy enone (**77c**) which was reported to undergo acid catalysed rearrangement to 2-phenylfuran (**58c**), Scheme 28.¹⁰¹ No mechanism was reported for this transformation.

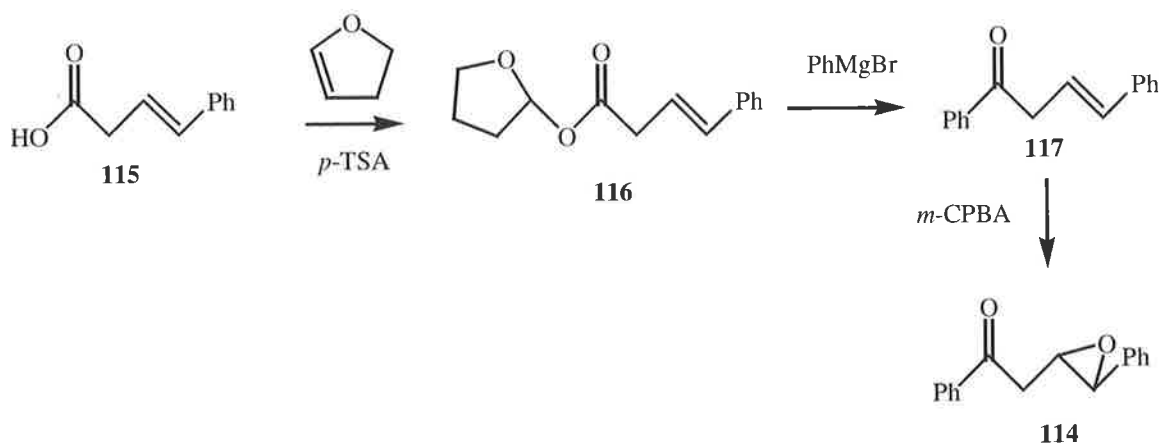
In a study conducted by Padwa *et al.* on the acid catalysed rearrangement of β,γ -epoxy ketone (**114**) to *cis* γ -hydroxy enone (**75a**) was proposed, Scheme 57.¹¹⁸ Subsequent cyclisation then of *cis* γ -hydroxy enone (**75a**) into its cyclic hemiacetals (*cis*-/*trans*-**76a**) and dehydration generated 2,5-diphenylfuran (**58a**). However, at no stage was there any direct spectroscopic observation of the *cis* γ -hydroxy enone (**75a**) or cyclic hemiacetals (*cis*-/*trans*-**76a**).

Scheme 57



In order to evaluate the β,γ -epoxy ketone as a source of 1,4-dicarbonyl, β,γ -epoxy ketone (**114**) was synthesised utilising a new rapid ketone synthesis from carboxylic acids via acyl hemiacetals, Scheme 58.¹¹⁹

Scheme 58



This procedure consisted of a one pot protection of acid (**115**) as the 2-tetrahydrofuranyl ester (**116**), followed by addition of phenylmagnesium bromide, which afforded the desired β,γ -unsaturated ketone (**117**) upon acidic workup. Epoxidation of unsaturated ketone (**117**) using *m*-CPBA gave the β,γ -epoxy ketone (**114**) of interest. Once synthesised, β,γ -epoxy ketone (**114**) was evaluated in the presence of various additives and ylides, Table 8.

Scheme 59

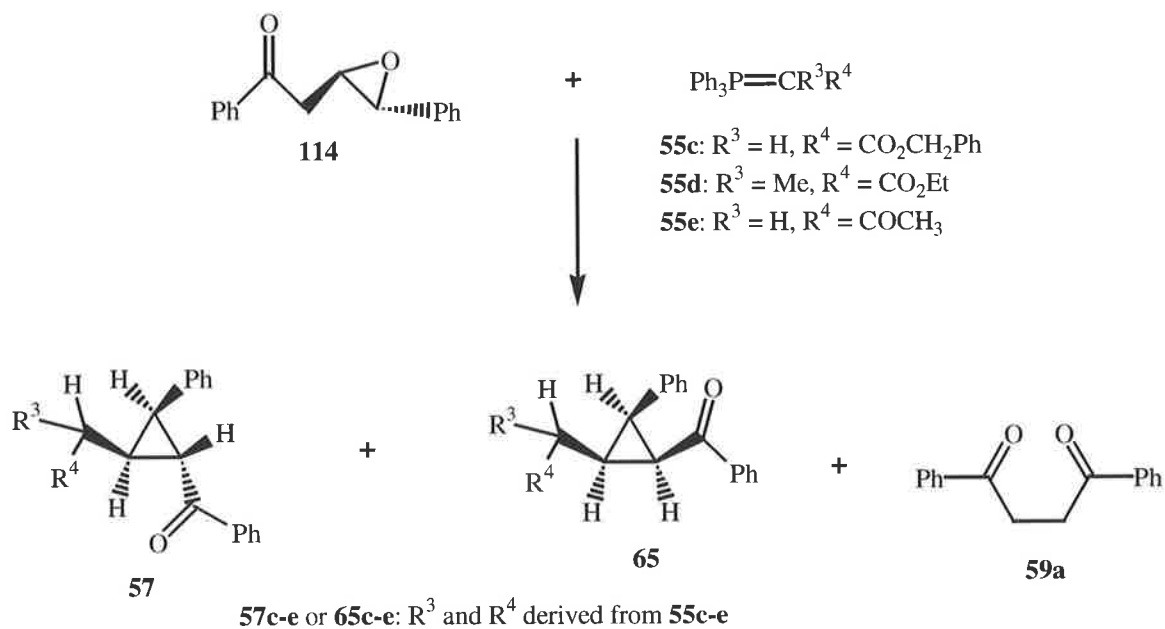


Table 8. Reaction of β,γ -Epoxy Ketone (114) with Additives and Stabilised Ylides (55c-e).^a

entry	ylide / additive	reaction time (d)	product(s); yield (%)
1	-	4	58a ; (100)
2	55c	14	57c ; (36), 59a ; (64)
3	55d	14	59a ; (100)
4	55e	5	59a ; (100)
5	TPPO	4	58a ; (100)
6	TPP	4	58a ; (100)
7	TEA	3	59a ; (100)
8	<i>p</i> -TSA	^b	58a ; (100)

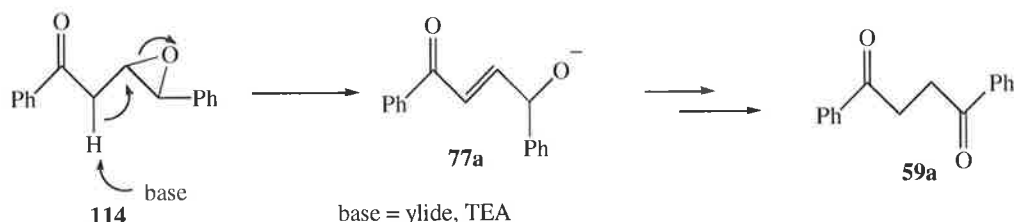
^a All reactions performed in CDCl₃ at a temperature of 50 °C unless otherwise stated. Yields were determined from the ¹H NMR spectra (300 MHz) of the crude reaction mixtures, isolated yields were typically within 10% of those reported. ^b Reaction time 5 minutes at ambient temperature.

In the absence of any additives β,γ -epoxy ketone (**114**) decomposed relatively slowly to give quantitative formation of furan (**58a**) at 50 °C. This rearrangement is, thus, consistent with the work of Padwa *et al.*, Scheme 57.¹¹⁸ Formation of furan (**58a**) from β,γ -epoxy ketone (**114**) was, however, relatively slow when compared to the rapid ambient temperature rearrangements of both *trans* (**77a**) and *cis* γ -hydroxy enones (**75a**) in their isolated states, discussed in Chapters 2 and 3 respectively. This result is inconsistent then with the idea that there is a β,γ -epoxy ketone intermediate allowing the *cis* / *trans* γ -hydroxy enone equilibrium to exist.

The reaction of β,γ -epoxy ketone (**114**) with ylide (**55c**) shown in entry 3 of Table 8 resulted in the formation of cyclopropane (**57a**) and 1,4-dicarbonyl (**59a**). Reaction of β,γ -epoxy ketone (**114**) with ylides (**55d,e**), entries 4 and 5 respectively, both resulted in quantitative 1,4-dicarbonyl (**59a**) formation.

Following the reactions of β,γ -epoxy ketone (**114**) with ylides (**55c-e**) by ¹H NMR showed the build up of *trans* γ -hydroxy enone (**77a**) in all cases, to about 10-20% of the reaction mixture. This result indicated that the reaction was proceeding through the *trans* γ -hydroxy enone, presumably due to the basic nature of the reactants, Scheme 60.

Scheme 60



Further support for this finding comes from the treatment of β,γ -epoxy ketone (**114**) with TEA, which resulted in quantitative conversion to the 1,4-dicarbonyl (**59a**). ^1H NMR monitoring demonstrated that 1,4-dicarbonyl (**59a**) formation proceeded through the *trans* γ -hydroxy enone (**77a**), with the β,γ -epoxy ketone (**114**) completely rearranged prior to reaction completion. Thus, it is evident that the action of base or ylide (acting as a weak base) causes rearrangement of the β,γ -epoxy ketone (**114**) into the *trans* γ -hydroxy enone (**77a**), from which 1,4-dicarbonyl (**59a**) arises, Scheme 60, instead of direct rearrangement into 1,4-dicarbonyl (**59a**).

The reactions of TPP and TPPO were performed in order to determine whether they contributed to the formation of 1,4-dicarbonyl (**59a**). Both reagents exhibited no effect upon the rearrangement of β,γ -epoxy ketone (**114**) into furan (**58a**), as in the control experiment, entry 1.

In conclusion it has been established that the β,γ -epoxy ketone (**114**) is not an intermediate existing within the equilibrium of the *cis* / *trans* γ -hydroxy enones (**75a** / **77a**). Rather, it represents an alternate method for the formation of cyclopropanes, via *trans* γ -hydroxy enones.

Origin of 1,4-dicarbonyl byproduct

As β,γ -epoxy ketones do not directly decompose to give 1,4-dicarbonyls, the problem of excessive 1,4-dicarbonyl formation when starting with *trans* γ -hydroxy enones remains.

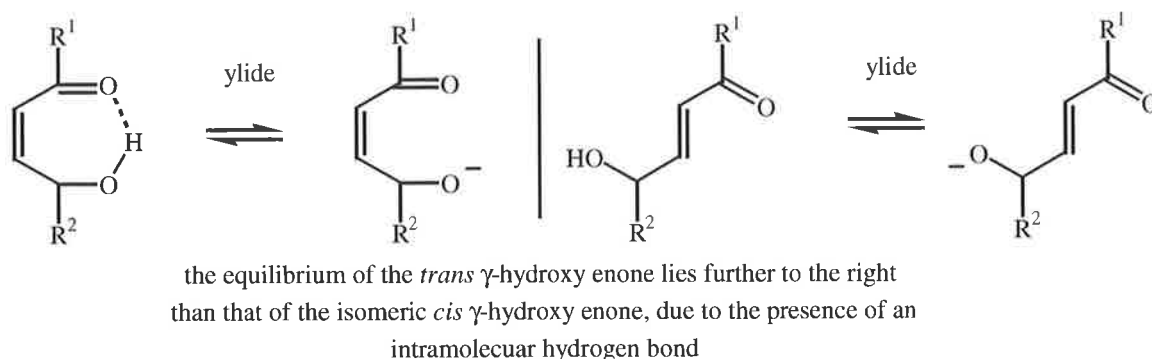
1,4-Dicarbonyls are generated within the reaction of stabilised phosphorus ylides and either 1,2-dioxines, *trans* γ -hydroxy enones or *cis* γ -hydroxy enones. In all cases the 1,4-dicarbonyls stem from base catalysed Kornblum-de la Mare rearrangement of the cyclic hemiacetals associated in equilibrium with their *cis* γ -hydroxy enones, Scheme 23. It was previously demonstrated that *cis* γ -hydroxy enones are generated from both 1,2-dioxines and *trans* γ -hydroxy enones as the key intermediates along the pathway to cyclopropanation. Therefore, there should be very little difference in product outcome when starting with either *cis* γ -hydroxy enones or *trans* γ -hydroxy enones. This, however, is not the case and considerable 1,4-dicarbonyl formation is observed during cyclopropanation utilising *trans* γ -hydroxy enones. The dramatic contrast is illustrated by comparing entry 1 of Table 7 (*cis* γ -hydroxy enone (**75a**)) and entry 1 of Table 5 (*trans* γ -hydroxy enone (**77a**)). In the case of the *cis* γ -hydroxy enone (**75a**), cyclopropane (**57c**) is generated in high yield (98%) with only minimal 1,4-dicarbonyl (**59a**) formation (2%). Conversely, with *trans* γ -hydroxy enone (**77a**), cyclopropane (**57c**) is generated in moderate yield (44%), with moderate 1,4-dicarbonyl (**59a**) formation (56%). Both these reactions were conducted under identical reaction volumes and concentrations. Naturally, as both reactions involve the use of the same ylide, the basic nature of the ylide cannot be contributing to the discrepancy.

It has previously been demonstrated that there are no intermediates influencing the reaction of *trans* γ -hydroxy enone and ylide and 1,4-dicarbonyl is generated through base catalysed rearrangement. Then in order to generate more 1,4-dicarbonyl there must be more base; or a stronger base present within the cyclopropanation reactions utilising *trans* γ -hydroxy enones as starting materials. Initially, the only base present within both the reactions of *cis* / *trans* γ -hydroxy enones with ylide are the ylides themselves. However, once added an acid / base equilibrium can be established with the γ -hydroxy enones. Consequently, the difference in basicity of the reactions can now be attributed to the variance in structure of the *cis* and *trans* γ -hydroxy enones and the effect this has on the acid / base equilibria of the cyclopropanation reactions.

In a review by Sadekov *et al.* the importance of intramolecular hydrogen bonding, within a molecule, on the acidity of the hydroxyl group has been highlighted.¹²⁰ Considering the structures of the *cis* and *trans* γ -hydroxy enones, it is proposed that intramolecular

hydrogen bonding of the hydroxyl group proton within the *cis* γ -hydroxy enone is extremely important. Therefore, due to intramolecular hydrogen bonding within the *cis* γ -hydroxy enone, the hydroxyl proton is held “tighter”, in comparison to that of the *trans* γ -hydroxy enone in which this type of intramolecular hydrogen bonding is absent, Scheme 61.

Scheme 61

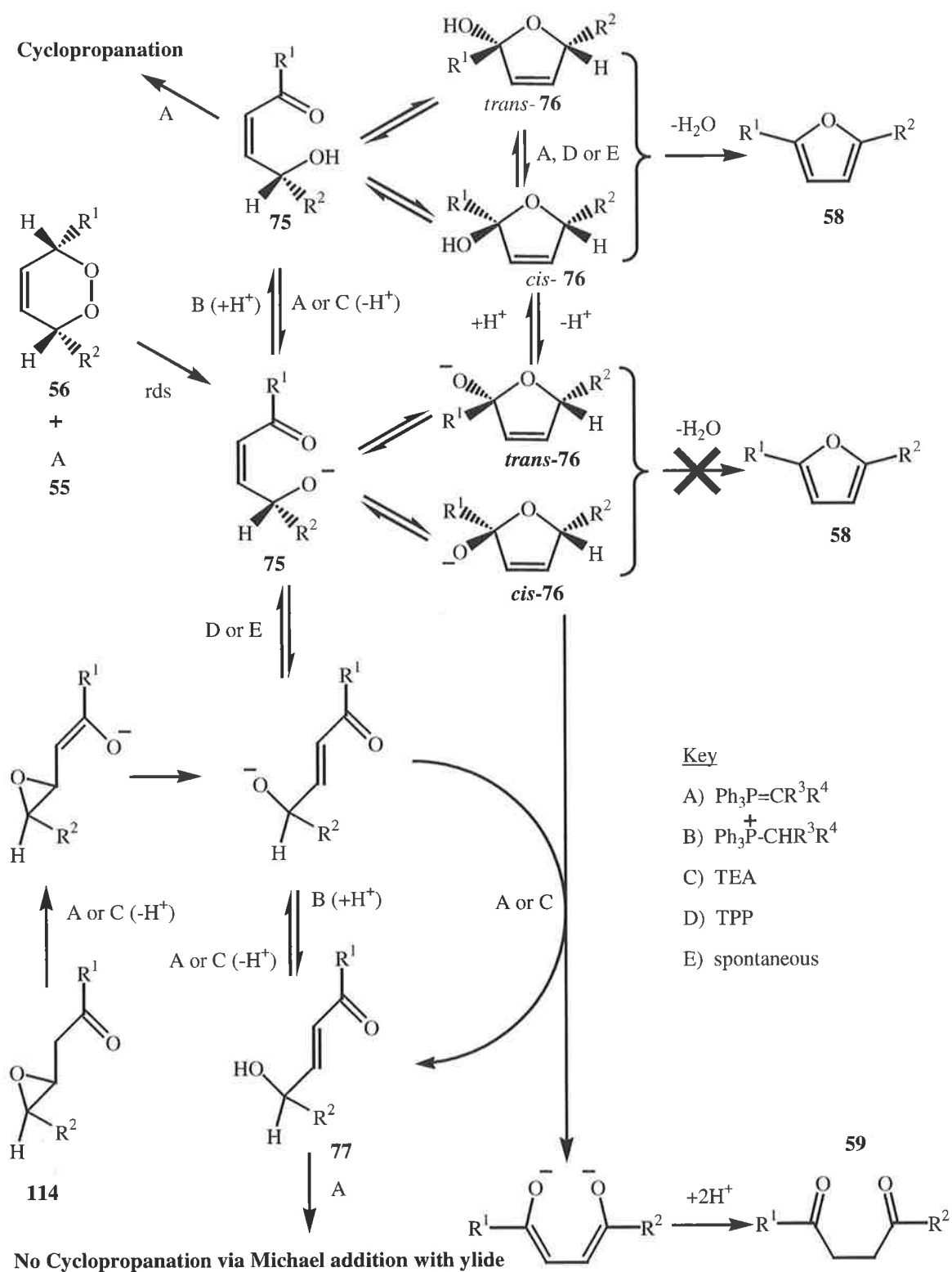


It is predicted then that in acid / base equilibria set up between the γ -hydroxy enones and the weakly basic ylides, there will be proportionally more of the *trans* γ -hydroxy enone anion than *cis* γ -hydroxy enone anion within their respective reactions. In this way, the *trans* γ -hydroxy enone anion generated can catalyse the formation of 1,4-dicarbonyl in the reaction of *trans* γ -hydroxy enones with stabilised phosphorus ylides.

Reaction Manifold

Now with an understanding of the origin of the 1,4-dicarbonyl (**59**) byproduct and the relationship between the isomeric 1,2-dioxines (**56**), *cis* / *trans* γ -hydroxy enones (**75** / **77**), *cis* / *trans* cyclic hemiacetals (*cis*-/*trans*-**76**) and β,γ -epoxy ketones (**114**) an overall mechanistic picture can now be drawn together, Scheme 62.

Scheme 62



Entering the manifold via the 1,2-dioxines (**56**), firstly involves regioselective removal of the most acidic proton α to the oxygen-oxygen linkage of the 1,2-dioxine (**56**) by ylide

(**55**) acting as a weak base. Rearrangement to the corresponding *cis* γ -hydroxy enone (**75**) ensues with concomitant reconstitution of the stabilised ylide (**55**).

cis γ -Hydroxy enones (**75**) exist in equilibrium with their *cis* and *trans* cyclic hemiacetals (*cis*-/*trans*-**76**), it is these isomers which are ultimately responsible for the formation of furan (**58**) and 1,4-dicarbonyl (**59**) byproducts. Acid catalysed dehydration of the *cis* and *trans* cyclic hemiacetals (*cis*-/*trans*-**76**) results in the formation of furans (**58**), however, furans (**58**) are not observed in the cyclopropanation due to the basic nature of the ylides (**55**). *cis* and *trans* cyclic hemiacetals (*cis*-/*trans*-**76**) generate 1,4-dicarbonyls (**59**) through the base catalysed Kornblum-de la Mare rearrangement, due to the presence of *cis* / *trans* γ -hydroxy enone anions within the reaction manifold. 1,4-Dicarbonyl (**59**) formation is most noticeable when entering the reaction manifold through the *trans* γ -hydroxy enones (**77**), or β,γ -epoxy ketones (**114**), both of which have been probed by individual synthesis. The reason for the increase in 1,4-dicarbonyl (**59**) is due to the formation of *trans* γ -hydroxy enone (**77**) anions in the reaction mixture. Anion formation does not effect the reaction proceeding from 1,2-dioxines (**56**) or *cis* γ -hydroxy enones (**75**) markedly. This is due to intramolecular hydrogen bonding of the hydroxyl proton within the *cis* γ -hydroxy enone (**75**), thus decreasing the likelihood of removal of the hydroxyl proton.

Further support for the reaction manifold comes from predictions that can be made. The increased 1,4-dicarbonyl (**59**) formation when proceeding through *trans* γ -hydroxy enones (**77**) can be avoided by choosing *trans* γ -hydroxy enones (**77**) whose *cis* isomer (**75**) exist in the absence of their *cis* / *trans* cyclic hemiacetals (*cis*-/*trans*-**76**). *cis* γ -Hydroxy enone (**75c**) exists without its hemiacetals and consequently we find that the corresponding *trans* γ -hydroxy enone (**77c**) when allowed to react with ylide presents negligible 1,4-dicarbonyl formation, entries 6 and 7 within Table 4.

Mechanism of cyclopropanation

In Chapter 1 an MIRC reaction mechanism was proposed for the formation of cyclopropane from 1,2-dioxines (**56**) and stabilised ylides (**55**), Scheme 24. The

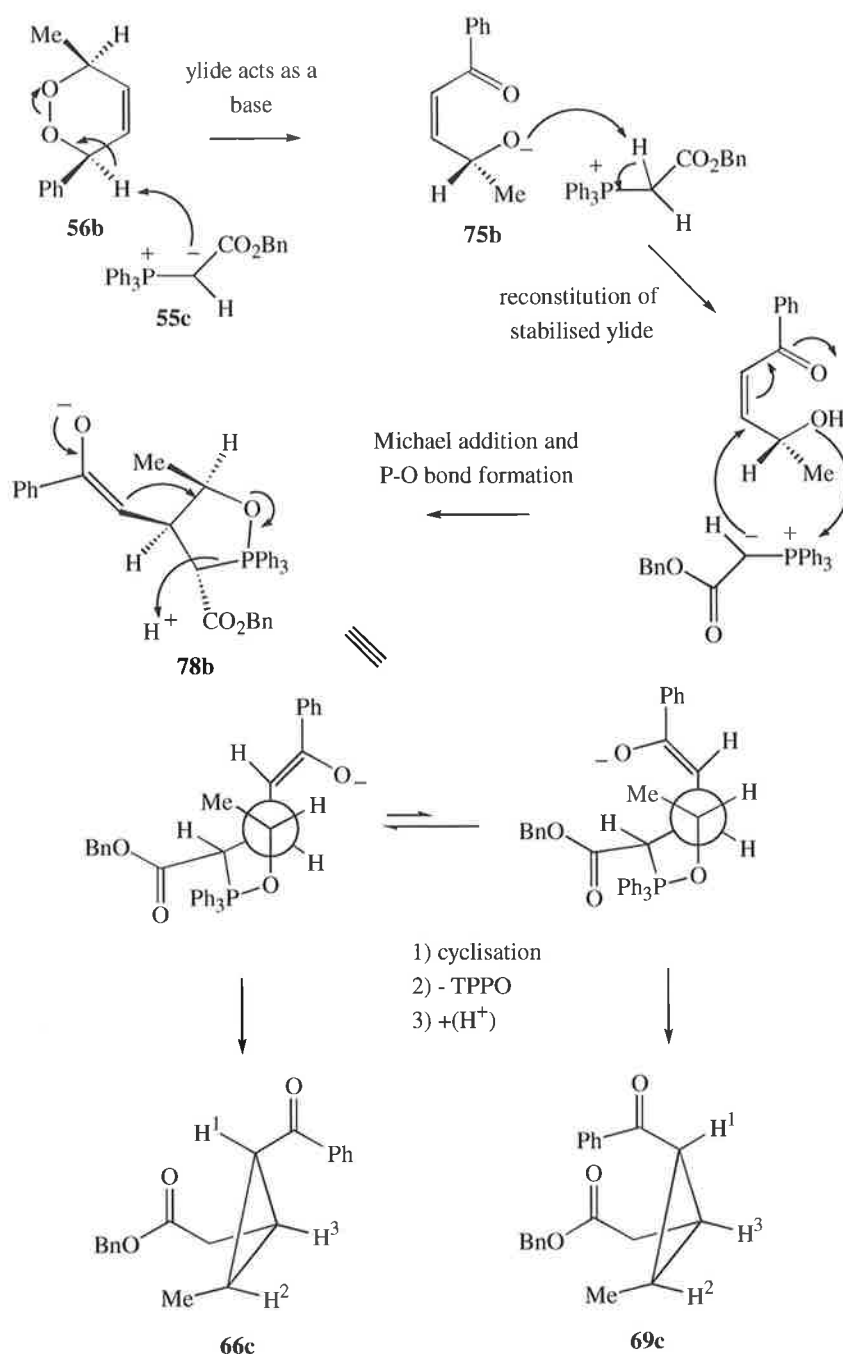
mechanism proposed that ylide (**55**) initially acts as a base in the removal of the proton α to the oxygen-oxygen linkage of the 1,2-dioxine (**56**) to generate the *cis* γ -hydroxy enone (**75**). It was then proposed that isomerisation to the *trans* γ -hydroxy enone (**77**) occurred with reconstitution of the stabilised ylide (**55**). Subsequently Michael addition of the ylide to the *trans* γ -hydroxy enone (**77**) resulted in the formation of the cyclopropanes.

Investigations outlined in Chapter 2, conducted into the use of *trans* γ -hydroxy enones (**77**) for cyclopropanation revealed that cyclopropane formation did not directly arise from the Michael addition of ylide (**55**) to the *trans* γ -hydroxy enone (**77**). It was subsequently shown, in Chapter 3, that it was the *cis* γ -hydroxy enone (**75**) that represented the key intermediate along the pathway to cyclopropane formation.

Utilising 1,2-dioxine (**56b**) and ylide (**55c**) as a specific example, Michael addition of the ylide (**55b**) to the *cis* γ -hydroxy enone (**75b**) occurs; accompanied by simultaneous oxygen-phosphorus bond formation resulting in the generation of the oxaphospholane intermediate (**78b**), Scheme 63. Cyclisation of enolate of (**78b**) with expulsion of TPPO results in the formation of both cyclopropyl isomers (**66c** and **69c**) the ratio of which depended upon the orientation of enolate collapse.

Drawing upon all the information now acquired a rationalisation for why keto-stabilised ylides do not undergo cyclopropanation is available. Subtle differences in the basicity / nucleophilicity of the ylides can be utilised to explain this variation.⁸⁶ While both ester and keto ylides alike enable base catalysed rearrangement of 1,2-dioxines, it is only the ester ylides which lead to cyclopropanes. Ester stabilised phosphorus ylides are better nucleophiles than the keto ylides and consequently undergo Michael addition more readily with the *cis* γ -hydroxy enones. Keto ylides on the other hand are slightly more basic than their ester counterparts, however, less nucleophilic, consequently, effecting the rearrangement of the *cis* γ -hydroxy enones to generate 1,4-dicarbonyl, in preference to undergoing cyclopropanation.

Scheme 63



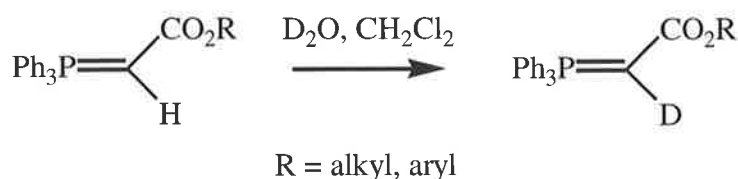
At this stage there is no direct evidence for the formation of the oxaphospholane intermediate (**78**) and its collapse through the enolate to form cyclopropanes. There has been no observation of the oxaphospholane intermediate when monitoring the reactions by either ^1H or ^{31}P NMR spectroscopy.

Cyclopropanation and D₂O

It was discovered in the early stages of research that the presence of water had no effect upon the formation of cyclopropanes. Therefore, it was envisaged that treatment of the reaction with deuterium oxide could enable refinement of the mechanism by following the position of deuterium incorporation within the reactants / products.

The literature contains several reports detailing the use of deuterium oxide and stabilised phosphorus ylides, of the type used in the discussed cyclopropanations.^{121,122} The general consensus is that the proton of the stabilised phosphorus ylide is highly exchangeable in the presence of deuterium oxide, Scheme 64.

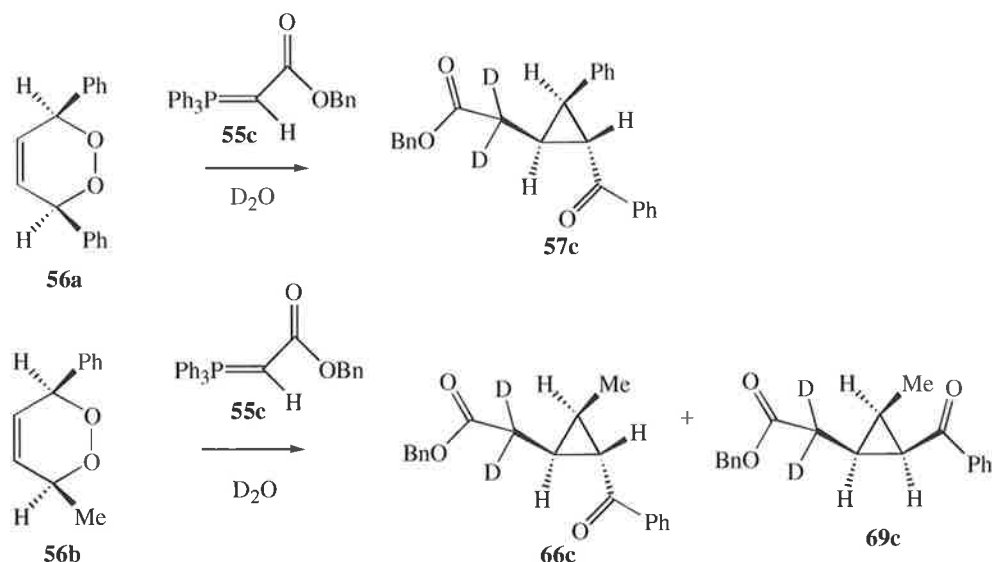
Scheme 64



It has previously been established in Chapter 3 that the hydroxyl group of the *cis* γ -hydroxy enone exchanges with deuterium oxide.

Initially the reaction of ylide (**55c**) with 1,2-dioxine (**56a**) was performed in the presence of excess deuterium oxide. Isolation and analysis by ¹H and ¹³C NMR showed cyclopropane (**57c**) to contain two deuterons located in the ester side chain, Scheme 65. Deuterium incorporation was determined to be > 95% by ¹H NMR. In order to determine generality of this reaction, ylide (**55c**) and 1,2-dioxine (**56b**) were allowed to react in the presence of deuterium oxide. As in (**57c**) two deuterons replaced the hydrogen atoms located in the side chain of the ester group in both cyclopropane isomers (**66c**) and (**69c**) as shown in Scheme 65.

Scheme 65

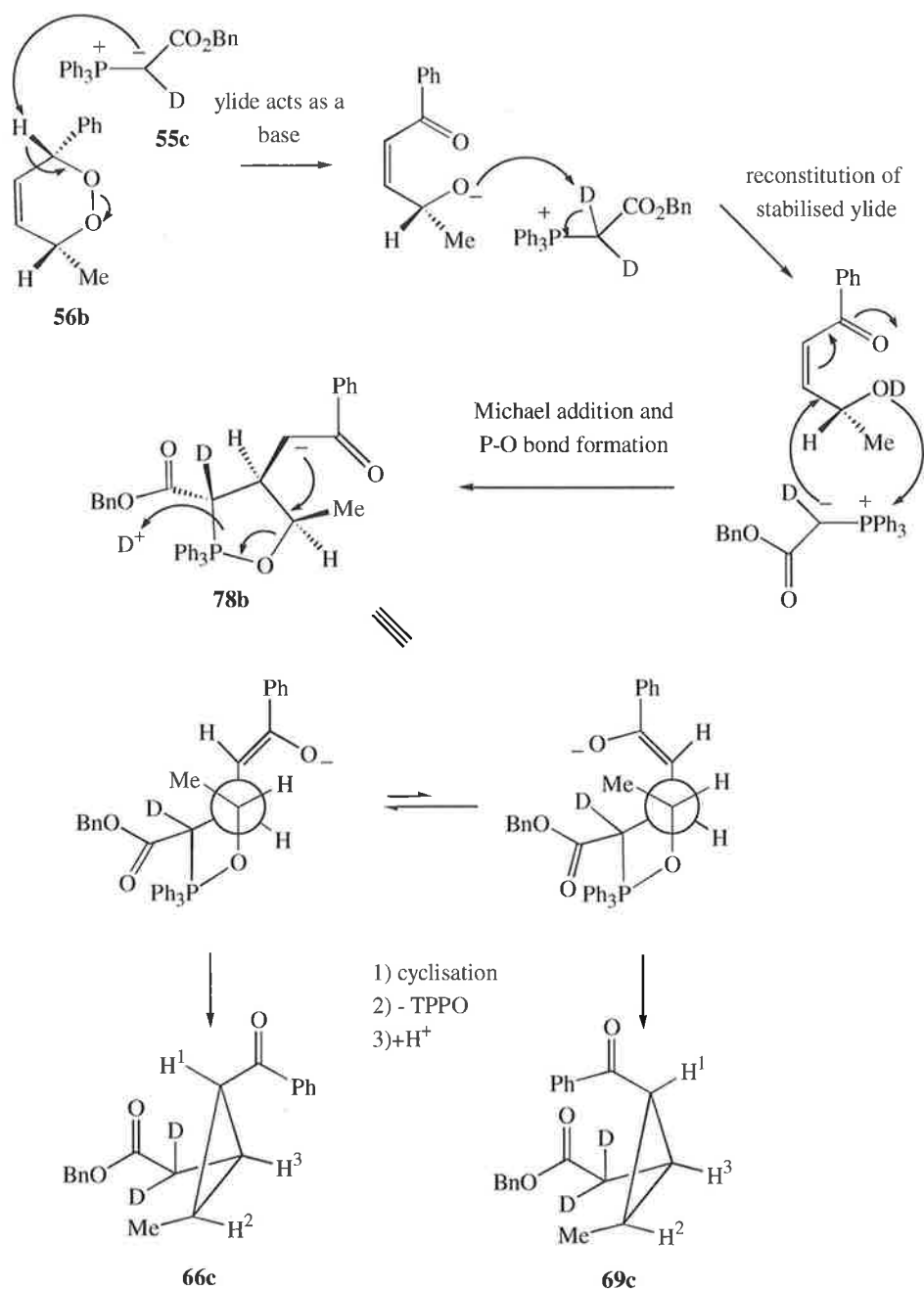


Deuterated cyclopropane (**69c**) was found to be significantly more stable than its protio analogue. There was no evidence of α,β -unsaturated ester (**72b**) formation via the enolene rearrangement at ambient temperature, Scheme 21. This is due to the increased bond strength of the D-C bond in comparison to the H-C bond.¹²³

To demonstrate that deuterium exchange occurs as a product reaction manifold and not just an exchange on the already formed cyclopropanes, cyclopropane (**57c**) was subjected to reflux in a D_2O / THF solution; no exchange was observed.

Applying the presence of excess deuterium oxide to the reaction mechanism, Scheme 66, it is seen initially that deuterium exchange on the ylide occurs, giving rise to deuterated (**55c**).

Scheme 66



The ylide (**55c**) acts as a base removing the α proton of the 1,2-dioxine (**56b**), which is also exchanged in the presence of deuterium oxide. Michael addition of the deuterated ylide to the deuterated *cis* γ -hydroxy enone results in the formation of the deuterated oxaphospholane intermediate (**78b**). Collapse of (**78b**) through the enolate, expulsion of TPPO with deuterium accounts for the formation of the two doubly deuterated cyclopropyl isomers (**66c**) and (**69c**).

The fact that the mechanism can account for the formation of the deuterated cyclopropanes lends greater support to the mechanism. It also demonstrates that the oxaphospholane enolate (**78b**) is not quenched during the reaction; this is demonstrated by the absence of deuterium substitution on the cyclopropane ring adjacent the phenyl ketone moiety. Consequently the oxaphospholane enolate (**78**) must have a limited lifetime and is consistent with the fact that no phosphorus species can be detected by ^{31}P NMR.

Summary and Conclusion

Research discussed within this and previous chapters have culminated in a clear mechanistic description of the interactions of isomeric 1,2-dioxines, *cis* / *trans* γ -hydroxy enones, *cis* / *trans* cyclic hemiacetals and β,γ -epoxy ketones and the formation of cyclopropanes.

β,γ -epoxy ketones, although not present in the reaction manifold as an intermediate within the equilibrium of *cis* / *trans* γ -hydroxy enones, represents another route to *trans* γ -hydroxy enones through base catalysed decomposition. Further work investigating the use of β,γ -epoxy ketones as precursors to cyclopropanes has been performed by *Heather Pain*.¹⁰⁹ The resulting work has allowed the synthesis of cyclopropanes otherwise unable to be synthesised via the 1,2-dioxine procedure.

The absence of intramolecular hydrogen bonding of the hydroxyl proton of the *trans* γ -hydroxy enone was responsible for its higher acidity. Thereby, resulting in a higher proportion of conjugate base present in the cyclopropanation reactions utilising *trans* γ -hydroxy enones as precursors instead of *cis* γ -hydroxy enones. The larger proportion of conjugate base was responsible for the increased 1,4-dicarbonyl, from the base catalysed Kornblum-de la Mare rearrangement, ratio present in these reactions.

An MIRC cyclopropanation reaction mechanism was proposed for the formation of cyclopropane; initiated via Michael addition of the ylide carbon pole to the *cis* γ -hydroxy enone. Formation of a transient oxaphospholane intermediate resulted, and through

collapse of oxaphospholane (**78**) and expulsion of TPPO the cyclopropyl isomers were generated. Incorporation of deuterium by allowing reaction of ylide and 1,2-dioxine in the presence of deuterium oxide provided confirmation of the proposed mechanism.

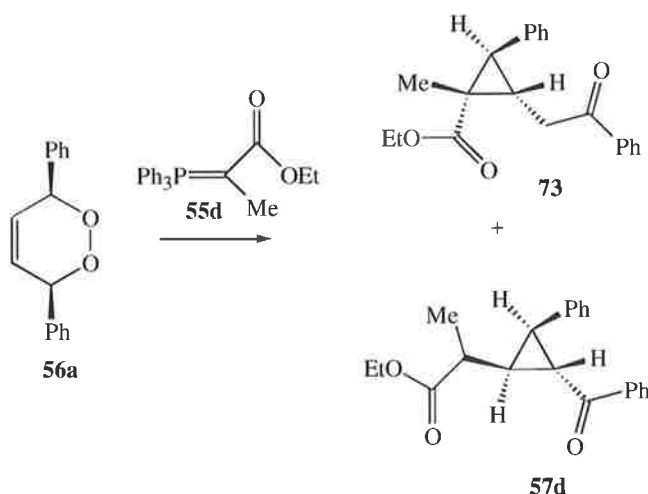
The ease of synthesis and non-exchangeable nature of deuterium once incorporated into the cyclopropane structure could enable their use as probes for enzyme mechanisms action and to follow biosynthetic/destructive pathways.¹²⁴ Tritiated and deuterated cyclopropanes have been used to synthesise cyclopropyl substrates and substrate analogues for use as probes of enzymatic mechanisms.¹²⁵⁻¹²⁷

Chapter 5: Sterically Hindered Ylides

Introduction

Previously, within the reaction of 1,2-dioxine (**56a**) and stabilised ylide (**55d**) it was noted that another cyclopropyl isomer was present, entry 2, Table 7. This isomer was tentatively assigned as ethyl 1-methyl-2-(2-oxo-2-phenylethyl)-3-phenyl-1-cyclopropanecarboxylate (**73**). The reaction was repeated on a large scale; cyclopropane (**73**) was isolated and determined, by extensive one- and two-dimensional ^1H and ^{13}C NMR experiments, to have a significantly different structure to cyclopropane (**57d**) also isolated.

Scheme 67



Considering the structure of the cyclopropane, the antecedent negative carbon pole of the ylide (**55d**) was incorporated into the ring of the cyclopropane (**73**) whereas previously this carbon atom was located within the ester side chain of the cyclopropane, as in (**57d**). It was consequently hypothesised that the sterically hindered nature of ylide (**55d**) was in some way responsible for the formation of cyclopropane (**73**). Therefore, an investigation into the use of bulky ylides within the cyclopropanation reaction was conducted.

Results and Discussion

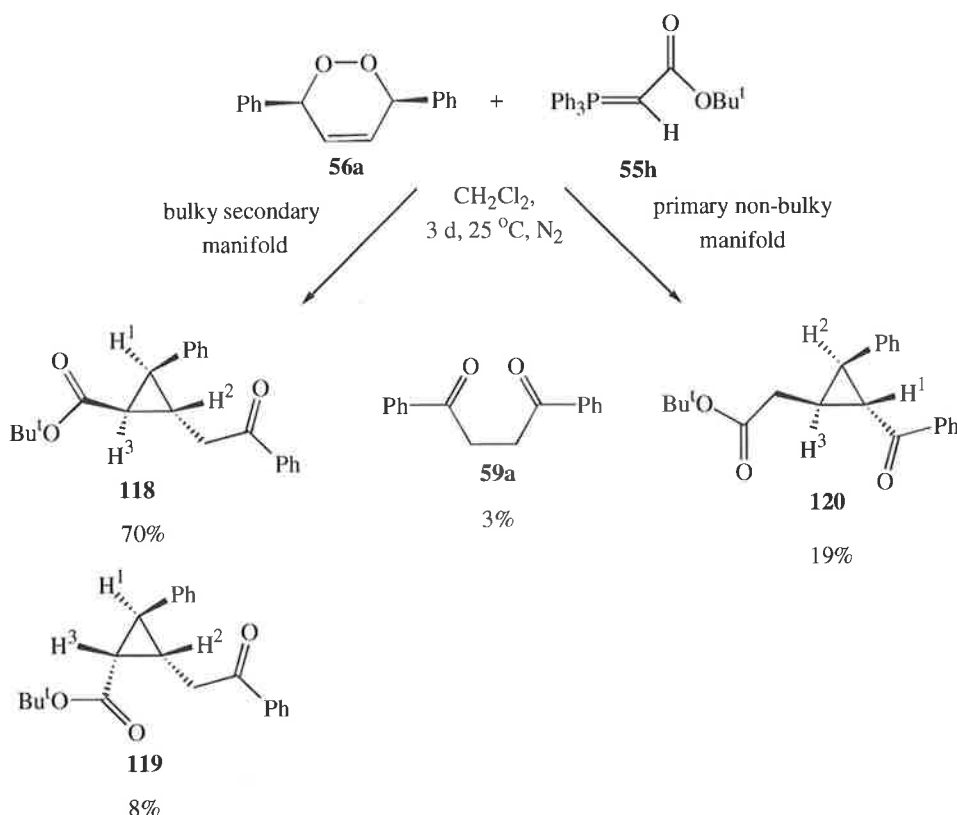
Discovery and structure

Use of the commercially available *t*-butyl ester ylide (**55h**) was decided upon due to its simple ^1H and ^{13}C NMR spectra. Ylide (**55h**) was allowed to react with 1,2-dioxine (**56a**), in dichloromethane at ambient temperature under an atmosphere of nitrogen. After three days, column chromatography upon the crude reaction mixture allowed the purification of three cyclopropyl isomers and 1,4-dicarbonyl (**59a**), Scheme 68. Extensive NMR and X-ray crystallographic (Appendix 2) studies revealed the structure of two of the cyclopropyl isomers to be diastereomers (**118**) and (**119**). These two cyclopropanes also contained the antecedent negative carbon pole of ylide (**55h**) incorporated into their cyclopropyl rings. The remaining cyclopropane (**120**) conferred identical stereochemistry and structure to the cyclopropanes resulting from the primary cyclopropanation manifold, which exploited non-bulky ylides.

The relative stereochemistry of the two cyclopropyl isomers (**118**) and (**119**) were assigned using the magnitudes of the couplings between cyclopropyl protons H^1 , H^2 and H^3 . Typical *trans* couplings of the ring protons within cyclopropanes (**118**) and (**119**) were around 4.8 Hz and the typical *cis* couplings at approximately 9.2 Hz.^{81,82} Examination of ^1H NMR spectrum of cyclopropane (**118**) revealed the magnitudes of $^3\text{J}_{1-2}$ and $^3\text{J}_{1-3}$ to be 5.4 and 9.6 Hz respectively, indicating a *trans* relationship to H^2 and a *cis* relationship to H^3 . H^3 exhibited couplings $^3\text{J}_{3-1} = 9.6$ Hz and $^3\text{J}_{3-2} = 4.8$ Hz indicating that H^3 was *cis* to H^1 and *trans* to H^2 .

Examination of the ^1H NMR spectrum of cyclopropane (**119**) revealed the magnitudes of $^3\text{J}_{1-2}$ and $^3\text{J}_{1-3}$ to be 5.4 and 6.6 Hz respectively, indicating a *trans* relationship to both H^2 and H^3 . H^2 exhibited couplings $^3\text{J}_{2-1} = 5.4$ Hz and $^3\text{J}_{2-3} = 9.6$ Hz indicating that H^2 was *cis* to H^3 and *trans* to H^1 .

Scheme 68



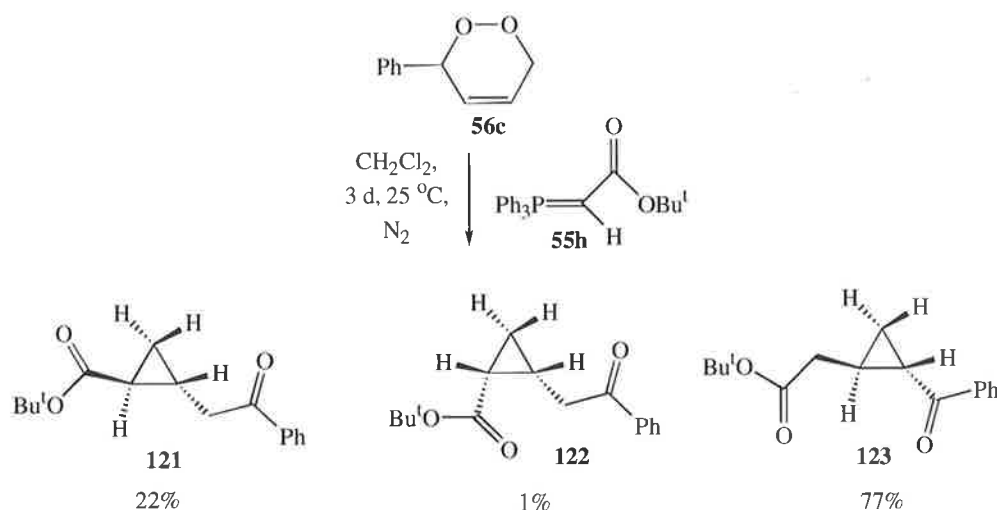
IR spectroscopy provided further support for the connectivity within the cyclopropyl isomers (**118**) and (**119**). Cyclopropane (**120**), resulting from the primary manifold exhibits peaks at 1733 cm^{-1} for an ester and 1656 cm^{-1} for an aryl ketone attached to a cyclopropane ring. The cyclopropanes resulting from the secondary manifold, which exploited bulky ylide (**55h**), displayed resonances at 1712 cm^{-1} for an ester attached to a cyclopropane ring and 1693 cm^{-1} for an aryl ketone.⁸¹

In order to discount the possibility that the cyclopropyl isomer (**118**) was arising from the isomer (**119**) via isomerisation or *vice versa* each isolated isomer was again allowed to react with ylide (**55h**) and TPPO under identical reaction conditions; no isomerisation was observed.

To establish the generality of this novel cyclopropanation, bulky ylide (**55h**) was allowed to react with 1,2-dioxine (**56c**). Once again three cyclopropyl isomers were isolated upon column chromatography of the reaction mixture. These were, as in the previous reaction

comprised of one cyclopropane resembling that of the primary manifold and two isomers resembling those of the secondary manifold, Scheme 69.

Scheme 69



Although the ratio of cyclopropanes arising from the primary and secondary manifolds varied greatly between the reactions of the different 1,2-dioxines (**56a,c**), clear major and a minor cyclopropyl isomer could be identified in each case.

In order to obtain a greater understanding of this second cyclopropanation manifold and how it relates to the previously discussed primary manifold, which exploited non-bulky ylides, investigations into the mechanism were initiated.

Effect of temperature and concentration

During the synthesis of cyclopropanes utilising the bulky *t*-butyl ylide (**55h**), variations in the ratio of the cyclopropanes arising from the primary and secondary cyclopropanation pathways became apparent. Experiments were consequently designed, to test the effect of concentration and temperature of the reactions of 1,2-dioxines (**56a,c**) and the bulky *t*-butyl ylide (**55h**). The results of these experiments are collated within Table 9.

Table 9. Effect of Temperature and Concentration on the Reaction of 1,2-Dioxines (56a,c) with Ylide (55h).

entry	1,2-dioxine	conc. (M)	temp. (°C)	solvent	products; yields (%) ^a
1 ^b	56a	0.08	-15	CDCl ₃	120 ; (0), 118 ; (91), 119 ; (9), 59a ; (0)
2 ^b	56a	0.12	25	CDCl ₃	120 ; (19), 118 ; (69), 119 ; (10), 59a ; (2)
3	56a	0.12	25	CH ₂ Cl ₂	120 ; (18), 118 ; (68), 119 ; (11), 59a ; (3)
4	56a	0.2	25	CH ₂ Cl ₂	120 ; (50), 118 ; (37), 119 ; (9), 59a ; (4)
5	56a	0.08	60	CDCl ₃	120 ; (33), 118 ; (52), 119 ; (6), 59a ; (9)
6 ^c	56c	0.12	-15	CH ₂ Cl ₂	123 ; (48), 121 ; (49), 122 ; (3), 59c ; (0)
7	56c	0.54	25	CH ₂ Cl ₂	123 ; (77), 121 ; (22), 122 ; (1), 59c ; (0)
8	56c	0.12	60	CDCl ₃	123 ; (81), 121 ; (14), 122 ; (5), 59c ; (0)

^a All ratios were determined via ¹H NMR (600 MHz) of the crude reaction mixtures. ^b Experiment was performed in the presence of 1 mol.% Jacobsen's catalyst; after 2 days at this temperature the sample was brought to room temperature for 1 day prior to analysis. ^c Experiment was performed in the presence of TEA (1 equiv.).

In order to compare the reactions within different solvents it was established that little variance in the cyclopropyl ratios is observed when utilising chloroform-*d* or dichloromethane as a solvent, this is demonstrated by comparison of entries 2 and 3, Table 9.

Through comparison of entries 1 and 5, and 6 and 8 it is evident that at constant concentration with increasing temperature, an increase in the proportion of cyclopropane arising from the primary manifold is observed. This is accompanied by a corresponding decrease in the proportion of cyclopropanes, arising from the secondary manifold. The

ratio of cyclopropanes, arising from the secondary manifold, however, remains essentially the same.

At elevated temperature an increase in the proportion of 1,4-dicarbonyl (**59**) byproduct is also observed, as expected, due to competing Kornblum-de la Mare rearrangement of the 1,2-dioxine (**56a**).

An increase in the proportion of cyclopropane arising from the primary manifold is also observed when the concentration of the reaction mixture is increased and the temperature held constant. This is illustrated by comparison of entries 3 and 4. Once again little change in the ratio of cyclopropanes arising from the secondary manifold is observed.

Therefore, the secondary cyclopropanation can be favoured over the primary manifold under conditions of low temperature and low overall concentration, entry 1.

Low temperatures presented problems in the formation of cyclopropane utilising 1,2-dioxines, as at temperatures below 0 °C 1,2-dioxines do not undergo rearrangement to *cis* γ -hydroxy enone in the presence of ylide. Furthermore, the formation of the cyclopropanes resulting from the bulky reaction pathway ceases at -30 °C. Consequently entries 1 and 6 were performed in the presence of cobalt catalyst and TEA respectively. Cobalt and TEA catalysis resulted in the formation of the *cis* γ -hydroxy enone at low temperatures, thus, cyclopropanation was made possible at low temperatures. Catalysed rearrangement of these reactions did not affect the ratio of cyclopropane formation, as entry 2 was also performed in the presence of cobalt catalyst whilst entry 3 was not. The rate of reaction, however, was increased in the presence of the cobalt catalyst.

Although the TEA catalysed cyclopropanation of 1,2-dioxine (**56c**) and ylide (**55h**) at -15 °C proceeded to form cyclopropane at this temperature (entry 6), the corresponding low temperature experiment involving 1,2-dioxine (**56a**) and ylide (**55h**) outlined in entry 1 did not. ¹H NMR analysis revealed the presence of two previously unidentified compounds which upon standing for two days at ambient temperature gave rise to cyclopropanes (**118**) and (**119**).

At this stage two competing reaction manifolds appear to be operating, although vastly different in outcome, both proceed through the intermediacy of the *cis* γ -hydroxy enone species to yield cyclopropanes.

Detection of intermediates A and B

Utilising the cobalt rearrangement technique, the reaction of *cis* γ -hydroxy enone (**75a**) and ylide (**55h**) was closely followed by ^1H NMR spectroscopy. Initially 1,2-dioxine (**56a**) was rearranged in CDCl_3 via the addition of 1 mol.% cobalt catalyst. An equimolar amount of ylide was then added and ^1H NMR spectra obtained every five minutes for the first thirty minutes and then every thirty minutes thereafter until reaction completion. During the twelve hour reaction, the formation of two intermediates was observed, intermediates **A** (**124**) and **B** (**125**). Intermediate **A** (**124**) formed first, while **B** (**125**) was observed to arise later, suggesting that **B** (**125**) was generated from **A** (**124**). The *cis* γ -hydroxy enone (**75a**) was consumed within four hours to yield intermediates **A** (**124**) and **B** (**125**), which over time gave rise to cyclopropanes (**118**) and (**119**). Some cyclopropane (**120**), arising from the primary manifold, was also observed within the reaction mixture, however, after consumption of *cis* γ -hydroxy enone (**75a**) formation of cyclopropane (**120**) ceased. This confirmed the presence of two distinct cyclopropanation pathways, one giving rise to cyclopropane (**120**) and the other proceeding through intermediates **A** and **B** resulting in the formation of cyclopropanes (**118**) and (**119**).

^{31}P NMR was used to analyse the reaction of 1,2-dioxine (**56a**) and ylide (**55h**), to determine whether the intermediates **A** (**124**) and **B** (**125**) contained phosphorus atoms and whether or not TPPO was released as a byproduct of the reaction. Two phosphorus peaks were observed at δ 23.99 and δ 24.29 ppm, Figure 11, paralleling the formation and relative ratios of intermediates **A** (**124**) and **B** (**125**) within the ^1H NMR spectra. Also observed was the formation of TPPO as the byproduct of the reaction. This was in stark contrast to the primary cyclopropanation reaction in which no phosphorus intermediates were observed.

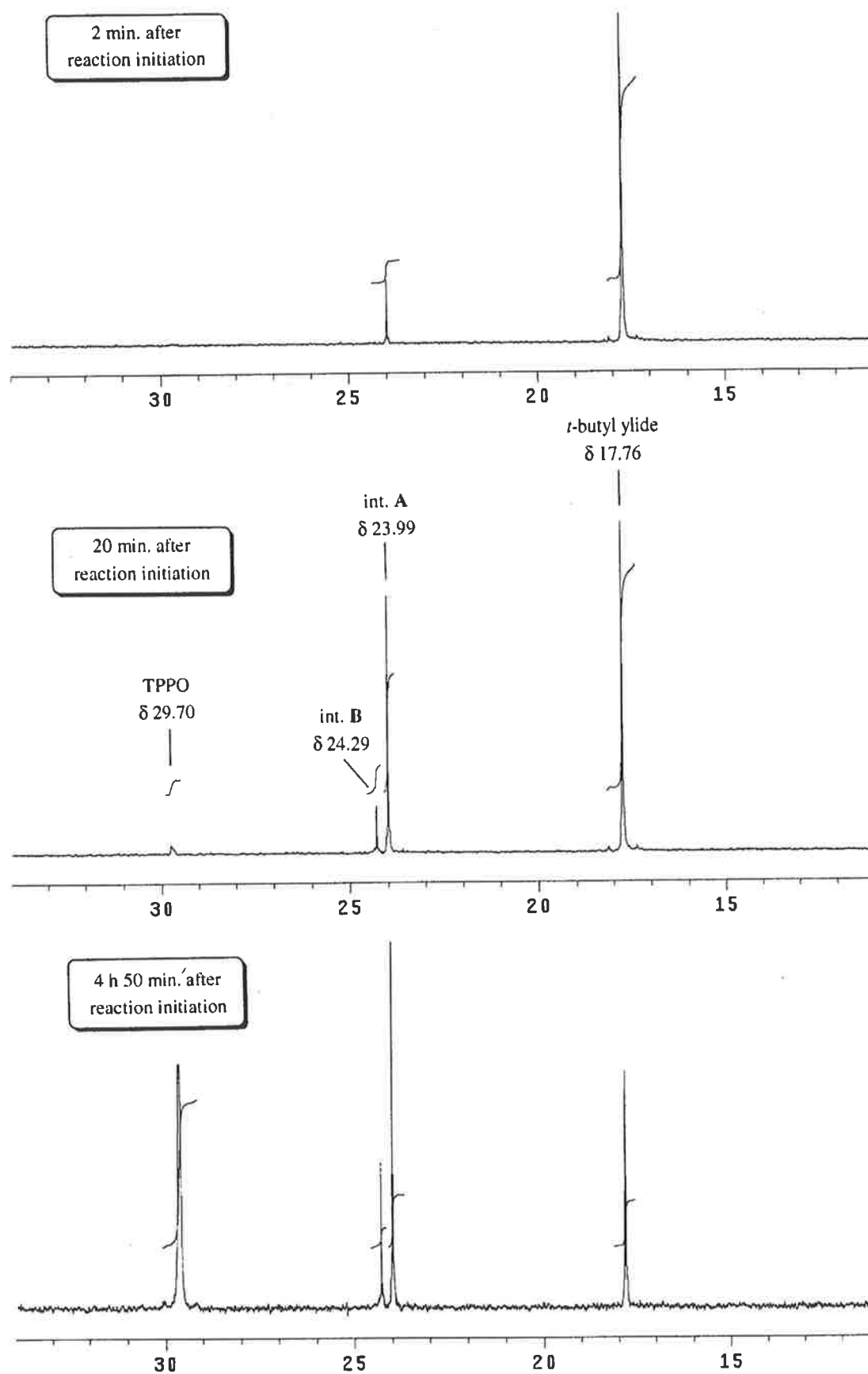


Figure 11. ^{31}P NMR spectra showing formation of intermediates **A** (**124**), **B** (**125**) and TPPO over time.

The ^{31}P NMR resonances observed for the intermediates **A** (**124**) and **B** (**125**) are inconsistent with those expected for a $1,2\lambda^5$ -oxaphospholane ring system, of the type proposed in the primary reaction manifold. An $1,2\lambda^5$ -oxaphospholane ring will typically exhibit a ^{31}P NMR resonance within the range of δ -40 to -60 ppm.¹²⁸⁻¹³¹ The resonances exhibited by intermediates **A** (**124**) and **B** (**125**) are more in line with charged species, with ylide characteristics. For example, the ^{31}P NMR resonance of the *t*-butyl ylide (**55h**) appears at δ 17.76 ppm, Figure 11.

Given that both intermediates **A** (**124**) and **B** (**125**) contain a *t*-butyl moiety, evident from ^1H NMR analysis, it was reasonable to conclude that both **A** (**124**) and **B** (**125**) are a hybrid of ylide (**55h**) and *cis* γ -hydroxy enone (**75a**) prior to the release of TPPO.

In order to elucidate the nature of intermediates **A** (**124**) and **B** (**125**) isolation of one or both of them for analysis was necessary. In the reaction of *cis* γ -hydroxy enone (**75a**) and *t*-butyl ylide (**55h**), entry 1 of Table 8, it was found that the intermediates were stable at -15 °C and none of the original cyclopropane was evident as a product within this reaction. This was due to the reasonably facile formation of intermediates **A** (**124**) and **B** (**125**) at this temperature with formation cyclopropanes from both primary and secondary cyclopropanation manifolds being extremely slow. Therefore, combining equimolar amounts of *cis* γ -hydroxy enone (**75a**) and ylide (**55h**) at -15 °C for two days resulted in quantitative formation of intermediate **A** (**124**) and **B** (**125**) in a ratio of 7 : 3 respectively. Subsequent extensive two dimensional NMR at -15 °C was carried out on the mixture. However, due to phosphorus coupling and complexity of the NMR spectra, structure elucidation was extremely difficult and more information was needed.

Isolation of intermediate B

In order to obtain either intermediate **A** (**124**) or **B** (**125**) in its pure state, generation of the intermediates was performed in various solvents. Deuterated solvents CDCl_3 ,

acetone- d_6 , benzene- d_6 , DMSO- d_6 and CD_3CN were used to enable rapid evaluation of the reaction mixtures by ^1H NMR. Intermediates **A** (**124**) and **B** (**125**) were generated over 2 days at $-15\text{ }^\circ C$ from equimolar amounts of *cis* γ -hydroxy enone (**75a**) and ylide (**55h**), however, on evaluation only minute variations in the ratio of intermediates **A** (**124**) and **B** (**125**) were detected.

Incredibly the solutions of intermediate **A** (**124**) and **B** (**125**) in benzene- d_6 , DMSO- d_6 and CD_3CN when brought to ambient temperature for 1 day deposited crystals. Upon analysis they were determined to be crystals of pure intermediate **B** (**125**). Dissolution in $CDCl_3$ for analysis resulted in intermediate **B** (**125**) establishing an equilibrium with intermediate **A** (**124**) in a ratio 3 : 7 respectively. Even though intermediate **B** (**125**) rearranges upon dissolving in solvent to intermediate **A** (**124**) and consequently cyclopropane, intermediate **B** (**125**), in its crystalline state is indefinitely stable at ambient temperatures. The crystals isolated from benzene- d_6 and DMSO- d_6 were of poor quality, however, the crystals generated from CD_3CN were spectacular and an X-ray crystal structure was obtained for intermediate **B** (**125**), Figure 12. Intermediate **B** (**125**) represents the first stabilised ylide to contain a hemiacetal moiety.

Extensive NMR studies were carried out on intermediate **B** (**125**) at $-15\text{ }^\circ C$ since equilibration to intermediate **A** (**124**) was slow at this temperature. This enabled the spectra of intermediate **A** (**124**) to be determined. Analysis of the ^{13}C NMR spectrum of **A** (**124**) showed it to have the same number of hydrogens and carbons as in **B** (**125**). Additionally intermediate **A** was determined to contain a ketone carbonyl showing resonance at δ 203.3 ppm, instead of a hemiacetal carbon atom as found in **B** (**125**) at δ 104.6 ppm. Comparison of the ^1H spin systems, through two dimensional NMR spectroscopy, of both intermediate **A** (**124**) and **B** (**125**), showed considerable similarity. This indicated that the connectivity of **A** (**124**) resembled that of **B** (**125**). Given the similarity of the phosphorus shifts it was supposed that intermediate **A** (**124**) also contains an ylide structure. Thus, the structure of intermediate **A** (**124**) was determined to be the acyclic form of intermediate **B** (**125**) as illustrated in Scheme 70.

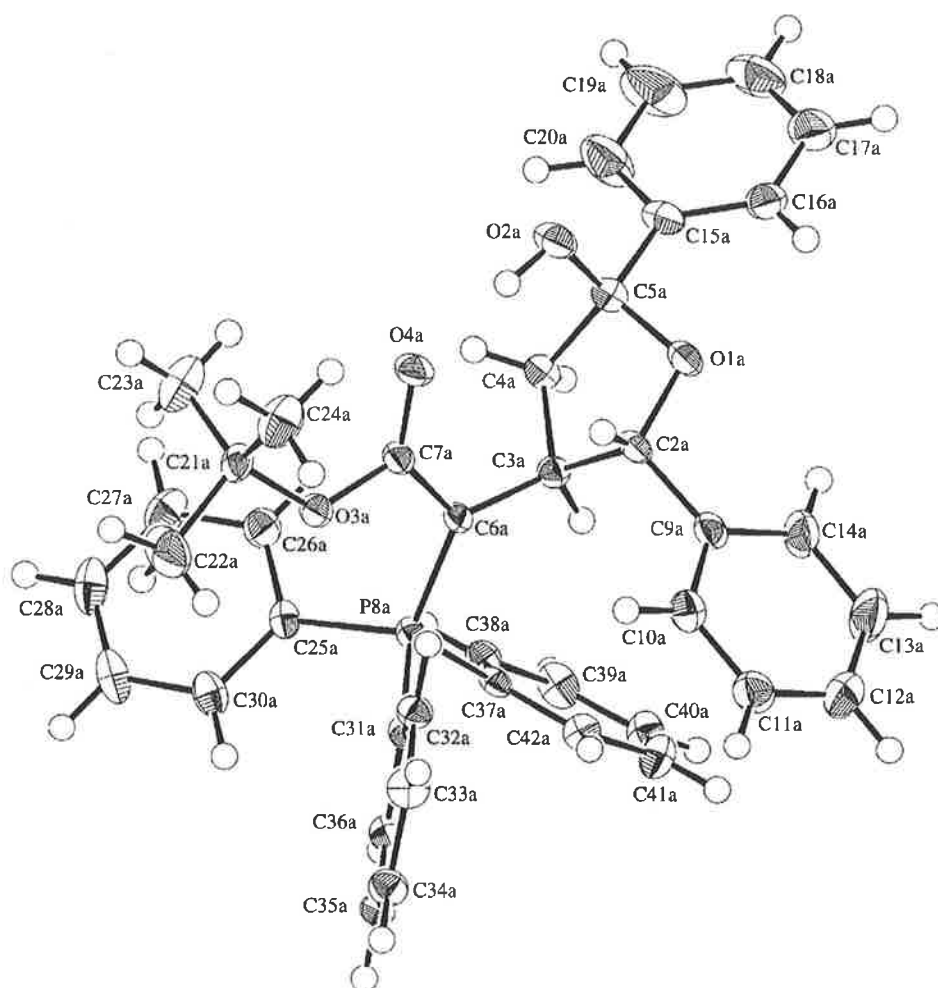
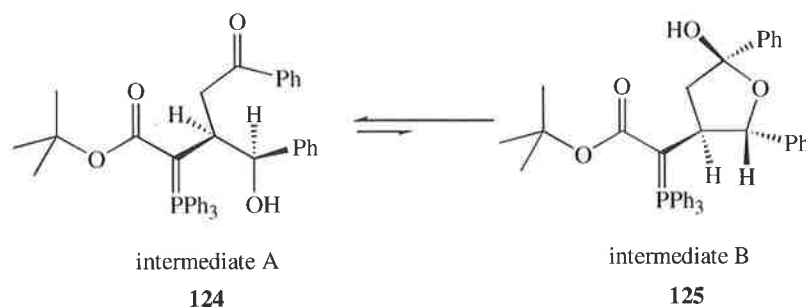


Figure 12. Molecular structure of intermediate **B** (125).

Scheme 70

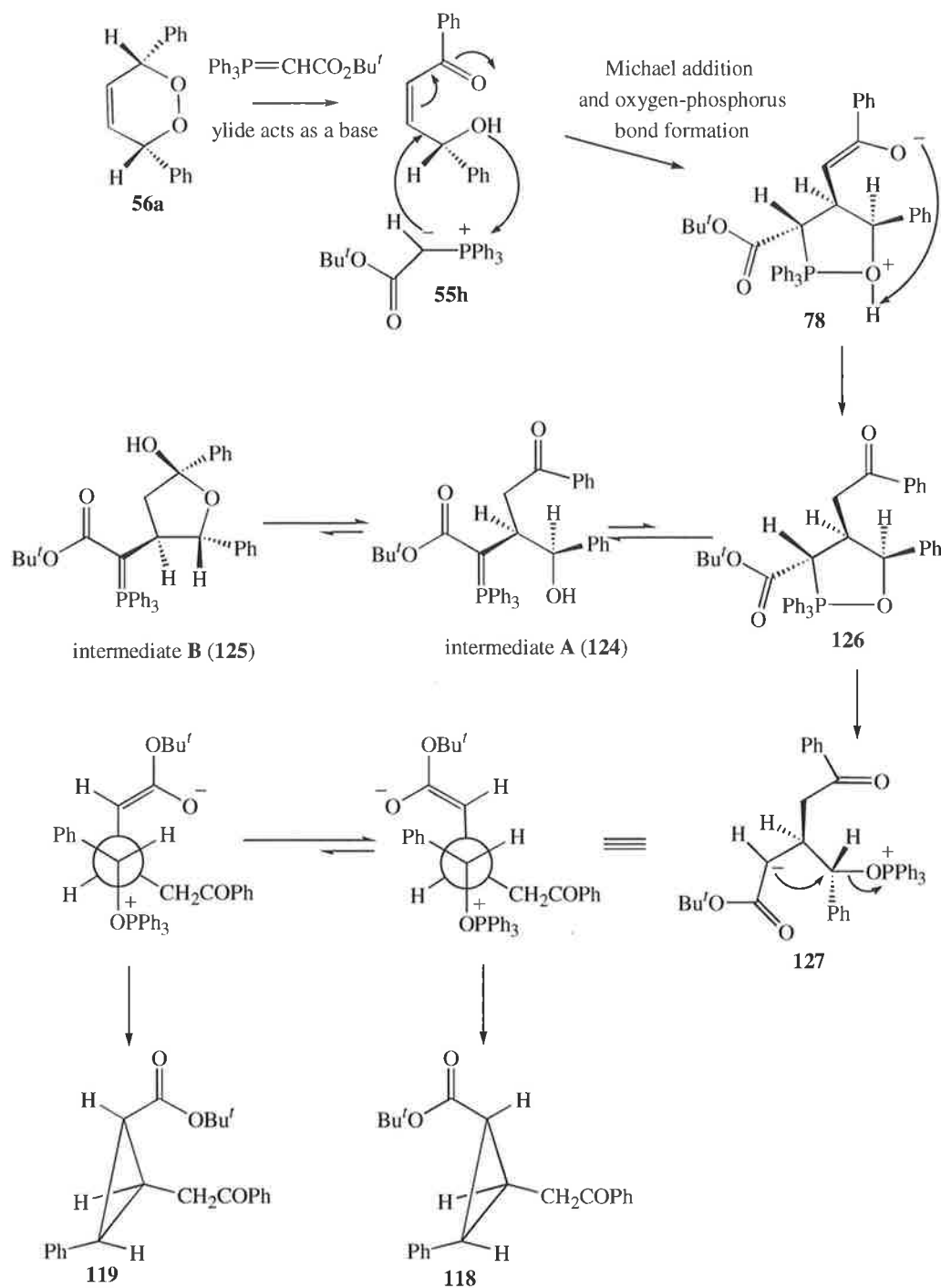


The structure of intermediate **A** (**124**) dictates that there should be, as in intermediate **B** (**125**), an exchangeable OH proton. However, no exchange other than the OH peak corresponding to the hemiacetal of intermediate **B** (**125**) was observed upon treatment of a solution of intermediates **A** (**124**) and **B** (**125**) with D₂O. Given the down field resonance of the OH proton of intermediate **B** (**125**) (δ 9.56 ppm), the OH proton of intermediate **A** (**124**) could conceivably be masked by the extensive aromatic regions of intermediates **A** (**124**) and **B** (**125**). It is known that in different deuterated solvents proton signals can be dramatically shifted.¹³² Therefore, ¹H NMR spectra of intermediates **A** (**124**) and **B** (**125**) were run in acetone-*d*₆, benzene-*d*₆, DMSO-*d*₆ and CD₃CN in an attempt to reveal the OH proton of intermediate **A** (**124**). The spectra obtained from DMSO-*d*₆ revealed a D₂O exchangeable proton at δ 6.67 ppm indicating that intermediate **A** (**124**) contained an OH moiety. This result was further confirmed by the use of ROESY NMR technique.

Mechanism of cyclopropanation

With the structure of the intermediates **A** (**124**) and **B** (**125**) established the mechanism for the formation of cyclopropane can be proposed, Scheme 71.

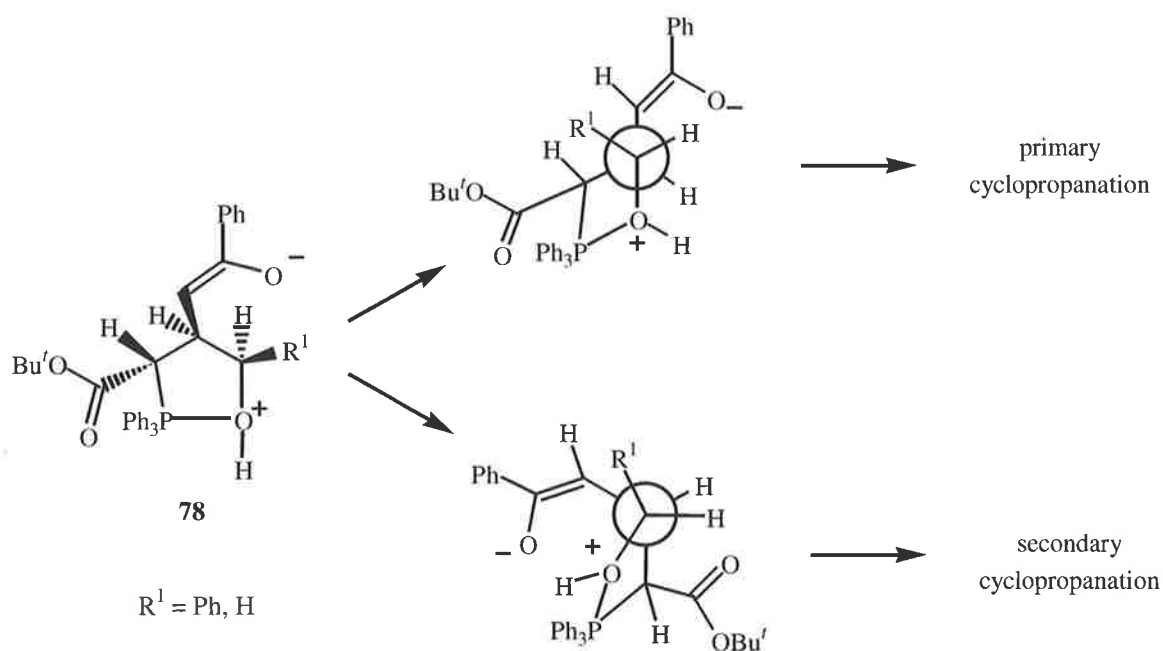
Scheme 71



As in the primary cyclopropanation, the reaction was initiated through ylide (**55h**) acting as a mild base inducing the regioselective ring opening of the 1,2-dioxine (**56a**) to give *cis* γ -hydroxy enone (**75a**). Michael addition with concomitant formation of an oxygen-phosphorus bond was proposed resulting in the formation of oxaphospholane (**126**).

Divergence from the primary cyclopropanation occurs with quenching of the enolate followed by oxygen-phosphorus bond fission of oxaphospholane species (**126**) to generate intermediate **A** (**124**). Intermediate **A** (**124**) then establishes an equilibrium with intermediate **B** (**125**). Enolate quenching instead of rearrangement to generate cyclopropanes from the primary manifold was due to the increased steric bulk of the ester side chain and its conformational influence upon the oxaphospholane ring (**78**). Alteration of the steric orientation of groups around the oxaphospholane ring makes enolate collapse through intramolecular S_N2 displacement of TPPO less favourable, as illustrated within Scheme 72. Thus, intramolecular quenching of the enolate becomes more favourable and generation of oxaphospholane (**126**) results. Following this reasoning, the favouring of the primary cyclopropanation over the secondary cyclopropanation at higher temperatures is due to the disruption of the lower energy conformation of the oxaphospholane ring (**78**), which leads to the cyclopropanes from the secondary cyclopropanation.

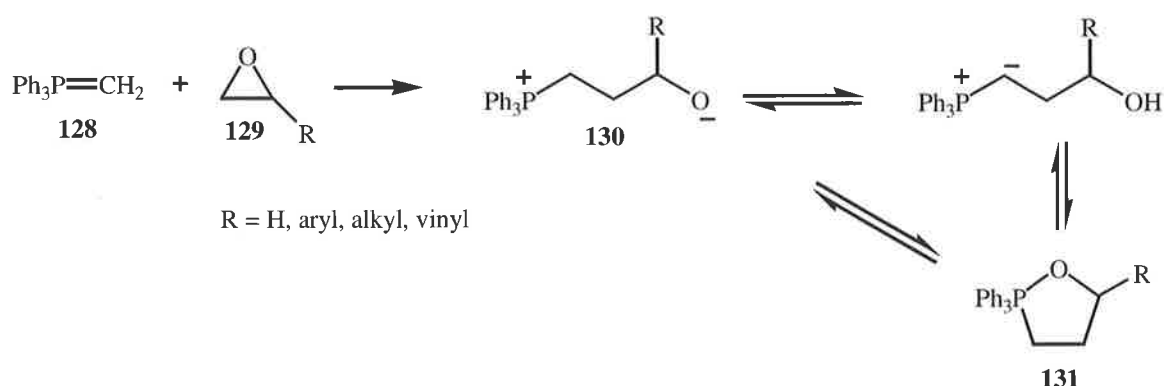
Scheme 72



The increased steric bulk of the *t*-butyl ester favours the conformation in which the enolate group is eclipsed by group R^1 , thereby preventing enolate cyclisation and favouring intramolecular enolate quenching.

Formation of intermediate **A** from oxaphospholane (**126**) requires oxygen-phosphorus bond fission. Reactions involving the formation of non-stabilised ylides from oxaphospholane rings via this type of ring fission have been reported in the literature.¹²⁸⁻¹³¹ These examples show the generation of ylides of the type shown in Scheme 73, from non-stabilised phosphorus ylides (**128**) and epoxides (**129**). The resultant ylides (**130**) exist in equilibrium with their oxaphospholane (**131**) counterparts, which in many cases are able to be isolated.

Scheme 73

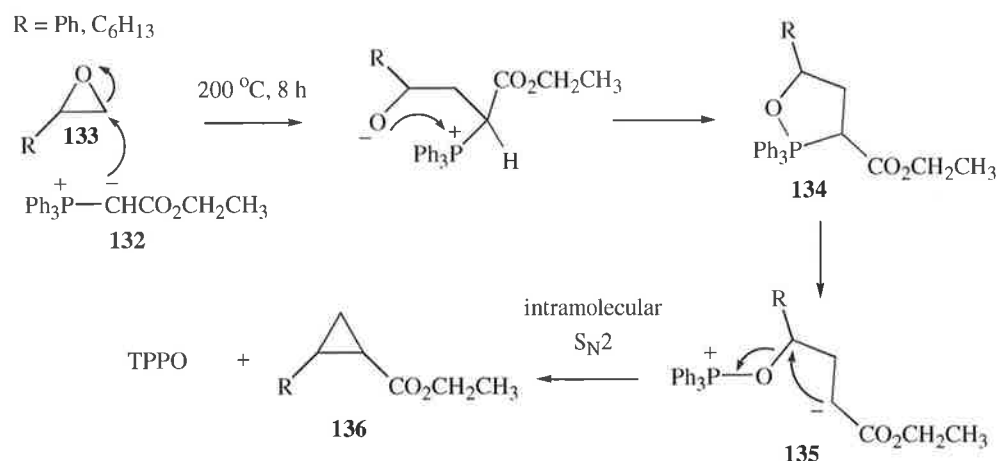


It is proposed that the intermediates **A** (**124**) and **B** (**125**) are not in fact necessary for the formation of cyclopropane. The formation of cyclopropane arises from oxaphospholane (**126**) through phosphorus-carbon ring fission to generate zwitterionic species (**127**). Compound (**127**) then undergoes intramolecular $\text{S}_{\text{N}}2$ expulsion of TPPO with formation of cyclopropane.

The structural orientation of species (**127**) during $\text{S}_{\text{N}}2$ expulsion of TPPO determines the stereochemistry of the two cyclopropanes (**118**) and (**119**). It is the steric interaction of the ester and ketone side-chains which determines the ratio of the two cyclopropanes.

Cyclopropanation via this type of carbon-phosphorus bond fission, of an oxaphospholane, has been reported previously. Denney *et al.* propose the formation of oxaphospholane (**134**) via a nucleophilic displacement reaction of stabilised ylide (**132**) on epoxides (**133**), Scheme 74. Ring opening generates zwitterion (**135**) which then undergoes intramolecular $\text{S}_{\text{N}}2$ displacement of TPPO to yield cyclopropane (**136**).

Scheme 74



Cyclopropanation and D₂O

In order to substantiate the mechanism outlined in the previous section the interaction of bulky ylide (**55h**) and 1,2-dioxine (**56a**) was probed with D₂O. The findings of these experiments are summarised in Table 10.

Firstly, the reaction was performed in the presence of water to determine the moisture sensitivity of the reaction shown in entry 2, Table 10. In comparison to the reaction in the absence of water, entry 1, the yield of cyclopropane arising from the primary cyclopropanation is markedly increased at the expense of the cyclopropanes from the secondary manifold. Despite the decrease in yield of cyclopropanes arising from the secondary manifold, it appeared that the presence of D₂O should still enable the formation of deuterated cyclopropanes.

As with the primary cyclopropanation one would expect that ylide (**55h**) would also undergo rapid H - D exchange, to generate the deuterated ylide, Scheme 64.^{121,122} It was discovered, however, that probing of the interaction of ylide (**55h**) and 1,2-dioxine (**56a**) with D₂O resulted in a considerable amount of ylide decomposition, entry 3, Table 10. Treatment of ylide (**55h**) with D₂O in CH₂Cl₂ resulted in complete decomposition of the ylide (**55h**) within 2 days at 40 °C. Utilising ³¹P, ¹³C, ¹H NMR spectroscopy to analyse

the crude reaction mixture, the products were revealed to be TPPO and *tert*-butyl acetate- d_3 (**137**) on comparison with the spectra of known samples, Scheme 75.¹³³

Scheme 75

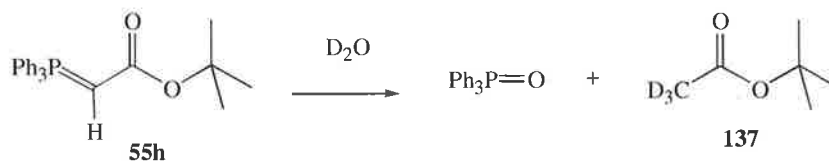


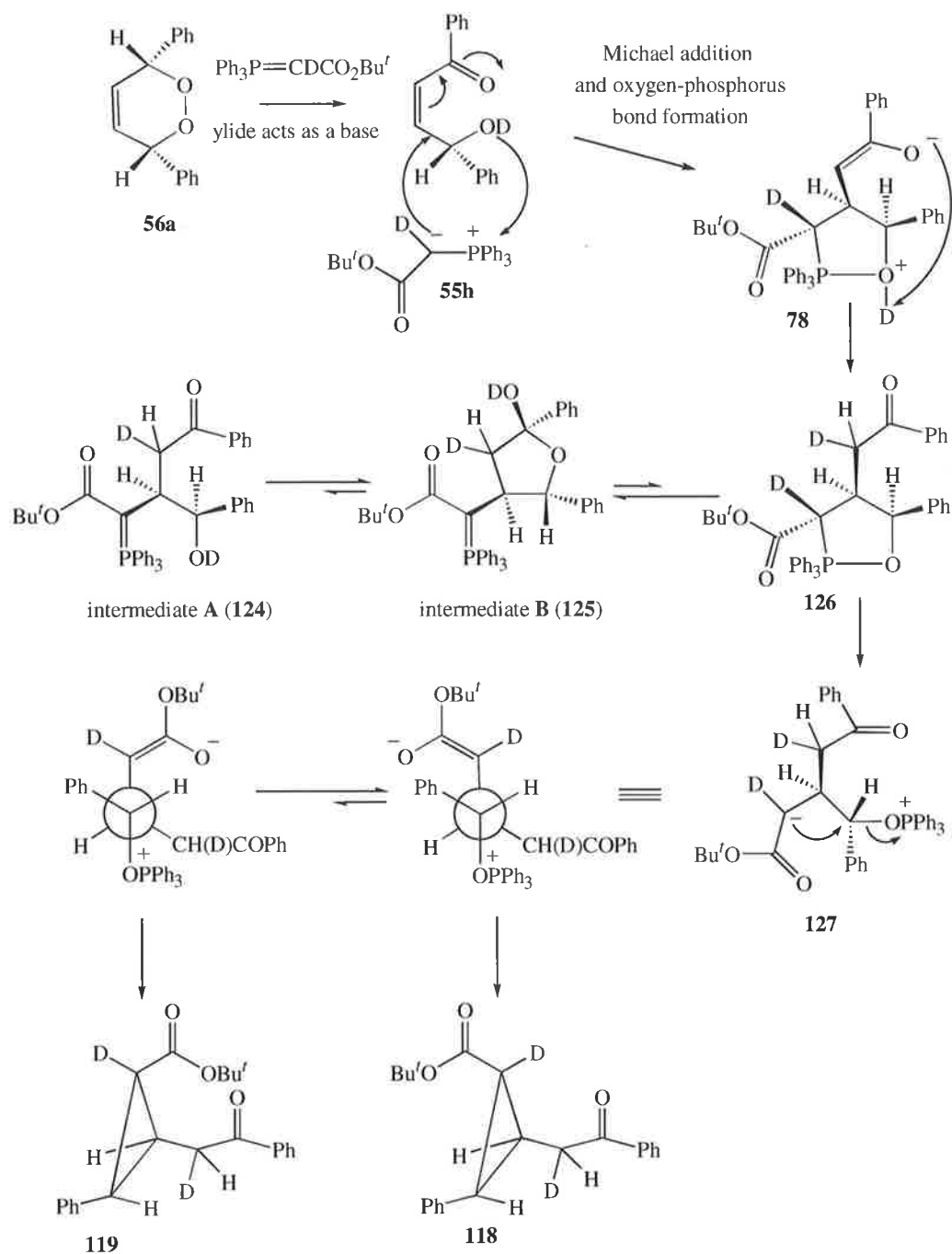
Table 10. The Effect of H_2O and D_2O Upon the Formation of Cyclopropanes (118**) and (**119**).^a**

entry	starting materials	reaction time	product(s); yields(%)
1	(75a), (55h)	5 days	120 ; (2), 118 ; (85), 119 ; (11)
2	(75a), (55h), H_2O	4 days	120 ; (41), 118 ; (56), 119 ; (1)
3	(56a), (55h), D_2O	4 weeks	120 ; (77), 118 ; (17), 119 ; (6)
4	(75a), (55h), D_2O	5 days	as for experiment 3
5	int. A/B	5 days	118 ; (80), 119 ; (20)

^a All reactions performed at identical concentrations at ambient temperatures in CH_2Cl_2 . Product ratios determined from ^1H NMR spectra (300 or 600 MHz) of the crude reaction mixtures.

Applying deuterium substitution to the hypothesised reaction mechanism, the *cis* γ -hydroxy enone (**75a**) would also be deuterated, so a reaction between this and the deuterated ylide would result in the formation of deuterated oxaphospholane (**78**), Scheme 76.

Scheme 76



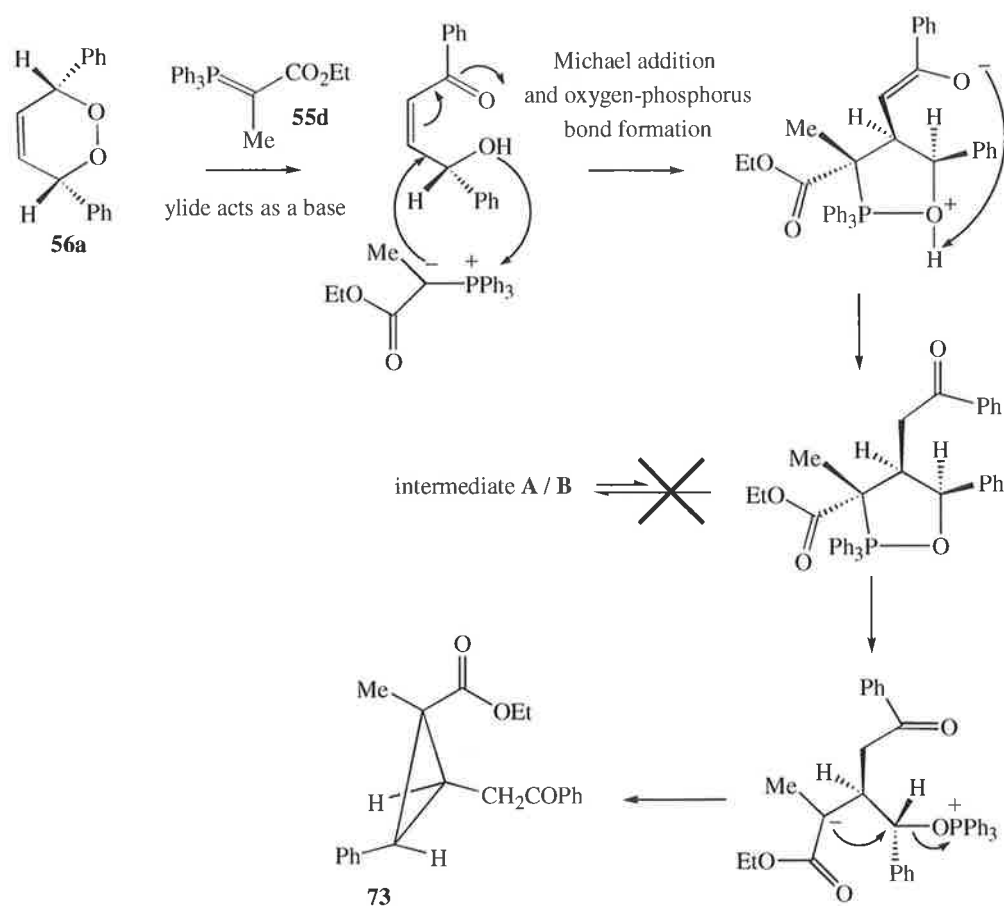
Quenching of the enolate would then result in the incorporation of a deuterium within the aryl ketone side chain. Rearrangement into cyclopropane expulsion of TPPO would then result in the doubly deuterated cyclopropanes (**118**) and (**119**).

Cyclopropanation in the presence of D₂O was found to favour the formation of cyclopropanes from the primary cyclopropane manifold to an even greater extent than treatment with water. This can be accounted for by the increased strength of oxygen-deuterium bond,¹²³ which increases the energy barrier to the formation of species (**126**), via intramolecular enolate quenching.

The fact that the presence of D₂O and H₂O favours the primary cyclopropanation manifold is due to hydrolytic deprotonation of the oxygen atom located in the ring of oxaphospholane (**78**). Deprotonation at this point would disfavour the intramolecular quenching of the enolate and, thus, favour the formation of the cyclopropanes arising from the primary manifold. On a parallel with this was the observation that cyclopropanation through the primary manifold is favoured by an increase in the concentration of the reaction mixture, Table 9. With an increase in concentration comes an increase in the proportion of stabilised ylide able to cause deprotonation of the oxaphospholane (**78**), in the same way as in the presence of water or D₂O.

Alternatively the proton adjacent the ester side chain of the oxaphospholane ring could be removed in quenching of the enolate. However, if this proton was responsible for enolate quenching in an intramolecular hydrogen transfer then water should have no effect upon the reaction. The formation of cyclopropane (**73**) from the interaction of ylide (**55d**) and 1,2-dioxine (**56a**) provides support for this, as the proton in question is substituted with a methyl group, Scheme 77. This is also mechanistically important from the point of view that it precludes the formation of intermediates **A** and **B**, demonstrating that the intermediates are not necessary for cyclopropane formation.

Scheme 77

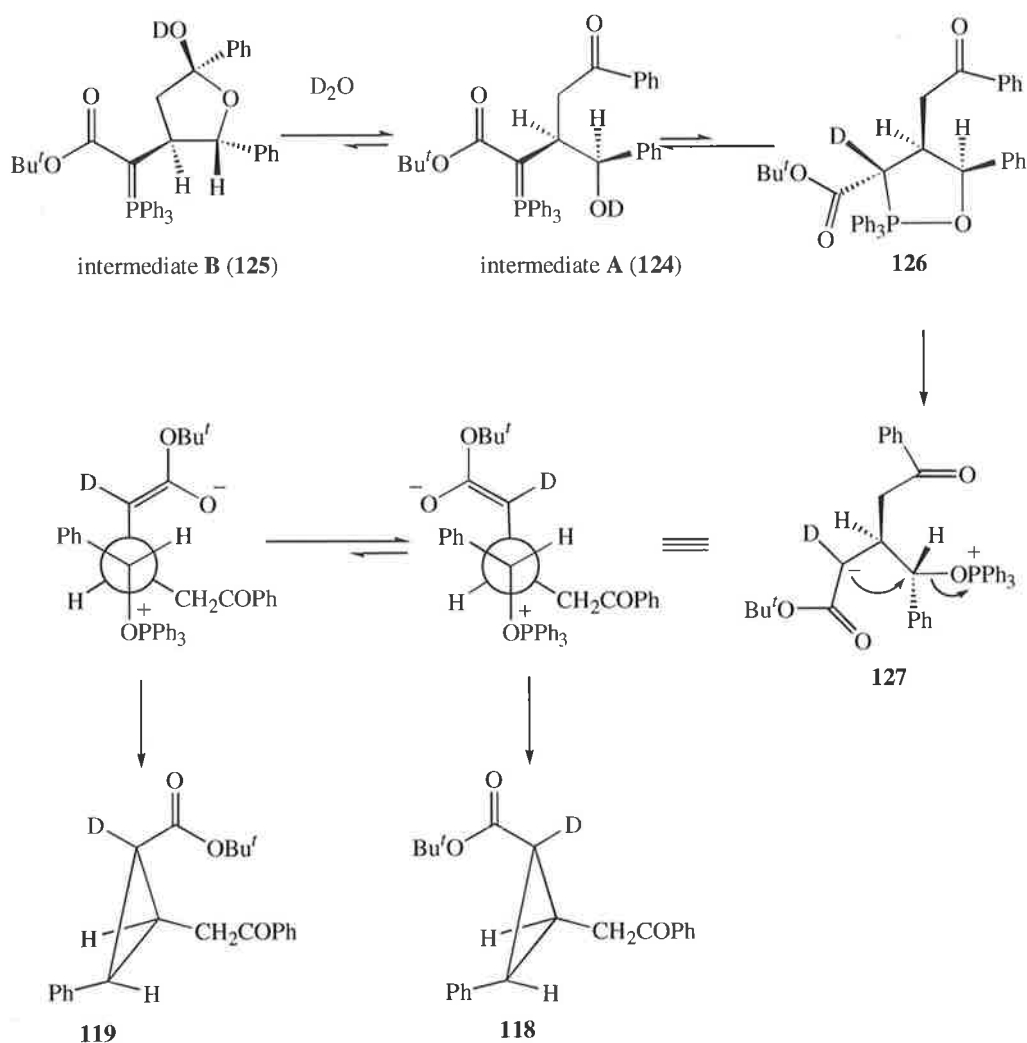


Analysis of the cyclopropyl products from entry 3 in Table 10, showed the cyclopropane (**120**) arising from the primary cyclopropanation manifold to be doubly deuterated in the ester side chain as predicted from studies in Chapter 4. This also confirms that this cyclopropane is arising from the primary manifold. The cyclopropyl isomers resulting from the secondary cyclopropanation were found to be deuterated once in the aryl ketone side chain resulting from quenching of the enolate and once in the ring of the cyclopropane adjacent the ester side chain hailing from original deuteration of the ylide. Deuterium incorporation was determined to be > 95% for in all cases by ^1H NMR. Both positions of deuteration are predicted by and provide substantial support for the proposed mechanism of cyclopropanation.

Treating a solution of intermediates **A** (**124**) and **B** (**125**) with D_2O under the same reaction conditions yielded the singly deuterated cyclopropanes (**118**) and (**119**).

Deuterium incorporation was located within the ring position adjacent the ester side chain, Scheme 78. This provides evidence for the reconstitution of oxaphospholane (**126**) prior to the formation of cyclopropane.

Scheme 78



All protonated cyclopropane analogues were subjected to treatment with excess D_2O in refluxing THF demonstrating that deuterium incorporation arises entirely from the reaction manifold.

Utilisation of temperature to alter cyclopropyl ratio

With methods for switching between the primary cyclopropanation and secondary cyclopropanation manifolds now available an investigation of the effect of temperature upon the ratio of cyclopropanes arising from the secondary manifold was initiated. The details of the temperature experiments are outlined within Table 11.

Table 11. Effect of Temperature on the Ratio of Cyclopropyl Isomers (118**) and (**119**).^a**

entry	precursor	solvent	temp. (°C)	reaction time	product(s); yield (%)
1	31a	CHCl ₃	-15 → 25	2 days + 2 days	118 ; (91), 119 ; (9)
2	31a	CHCl ₃	-15 → 60	2 days + 12 h	118 ; (63), 119 ; (37)
3	31a	toluene	-15 → 100	2 days + 6 h	118 ; (55), 119 ; (45)
4	int. B	CDCl ₃	25	2 days	118 ; (86), 119 ; (14)
5	int. B	CDCl ₃	70	12 h	118 ; (53), 119 ; (47)
6	int. B	neat	170	10 mins	118 ; (18), 119 ; (82)
7	int. B	neat	205	10 mins	118 ; (18), 119 ; (82)

^a All product ratios were determined from ¹H NMR spectra (300 or 600 MHz) of the crude reaction mixtures.

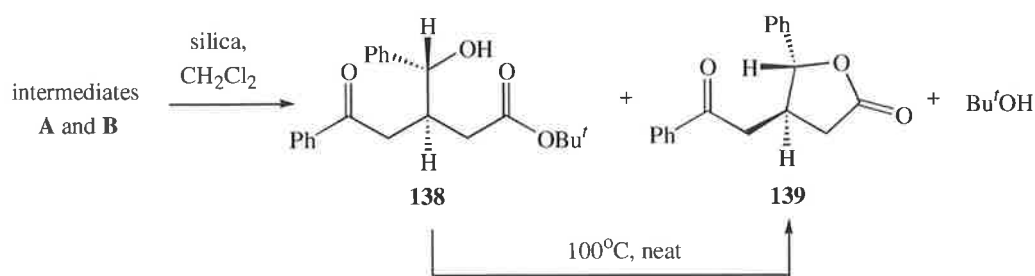
Initially mixtures of intermediates **A** (**124**) and **B** (**125**) were generated at -15 °C and then subjected to various temperatures as indicated in Table 11. Upon examination of the final product ratio of these reactions it can be seen that the proportion of the once minor cyclopropyl isomer (**119**) increases steadily with a corresponding increasing temperature. The effect became more pronounced when crystals of intermediate **B** (**125**) were heated in the solid state. Liquification of the crystals occurs at 156–158 °C with the maximum yield of cyclopropane (**119**) peaking at around 170 °C. Furthermore, both cyclopropyl isomers were subjected to temperatures above 200 °C for 10 minutes and showed no evidence of spontaneous stereomutation. This methodology opens up the previously minor isomer (**119**), from the secondary cyclopropanation reaction, to exploitation as a viable synthon for organic chemistry.

It is unclear at this stage as to why elevated temperatures would favour the formation of the cyclopropyl isomer (**119**).

Silica gel catalysed rearrangement of intermediates A and B

Given the importance of intermediates **A** (**124**) and **B** (**125**) in the formation of cyclopropane formation via the secondary manifold another method of isolating intermediates was studied. Attempted isolation by silica gel chromatography, resulted in the rearrangement of intermediates **A** (**124**) and **B** (**125**) into γ -hydroxy ketone (**138**) and lactone (**139**), Scheme 79.

Scheme 79



Upon heating γ -hydroxy ketone (**138**) to 100°C , lactone (**139**) and *t*-butyl alcohol were formed via attack of the hydroxyl group on the *t*-butyl ester. The relative stereochemistry of the two compounds was determined via X-ray crystallography of lactone (**139**).

Repeating the reaction, this time utilising crystals of intermediate **B** (**125**), the generation of γ -hydroxy ketone (**138**) and lactone (**139**) was followed by ^1H NMR spectroscopy. Addition of silica to a sample of intermediate **B** (**125**) resulted in the establishment of an equilibrium with intermediate **A** (**124**) within five minutes. This mixture then decomposed over forty five minutes to give the products (**138**) and (**139**).

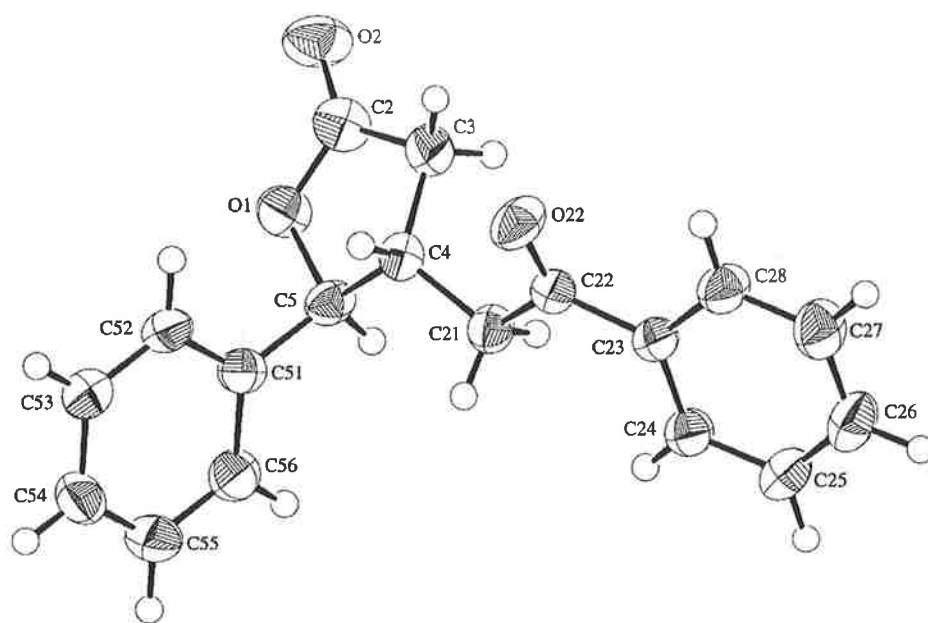
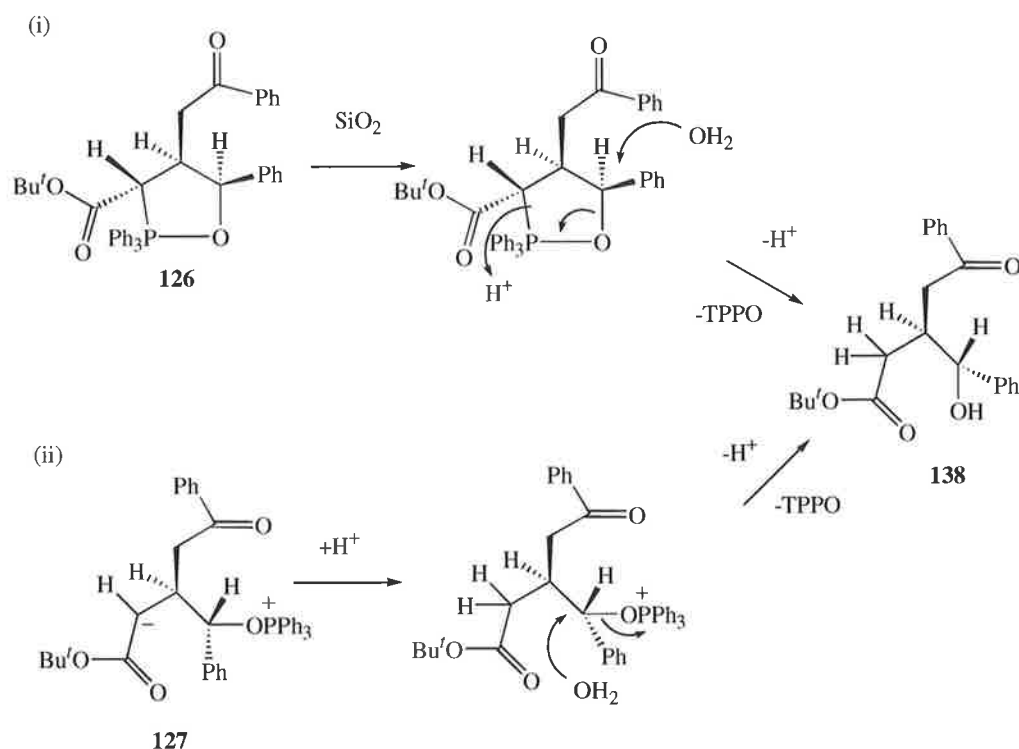


Figure 12. Molecular structure of lactone (139).

Analysis of the crude reaction mixture by ^{31}P NMR, revealed that the loss of phosphorus proceeded via the formation of TPPO and not TPP. Therefore, with the secondary cyclopropanation manifold established the mechanism for silica rearrangement was rationalised.

The open chain γ -hydroxy ketone (**138**) resembles the structure of intermediate **A** (**124**), with the absence of the triphenylphosphine group and inversion of the stereochemistry at the carbon adjoining the hydroxyl moiety. It was hypothesised then that formation of (**138**) can, therefore, proceed through (i) coordination of silica to oxaphospholane (**126**) followed by $\text{S}_{\text{N}}2$ attack by water, releasing TPPO or (ii) by protonation of (**127**) followed by $\text{S}_{\text{N}}2$ displacement of TPPO by water, Scheme 80. Both methods account for the inversion of stereochemistry at the carbon adjoining the hydroxyl group.

Scheme 80



Summary and Conclusions

The utilisation of bulky ester stabilised phosphorus ylide (**55h**) upon 1,2-dioxine (**56a**) has opened the way for the synthesis of two new cyclopropanes via a novel cyclopropanation mechanism. This related, secondary cyclopropanation, as in the primary manifold proceeds via Michael addition of ylide to *cis* γ -hydroxy enone resulting in the formation of an oxaphospholane ring. Divergence from the original cyclopropanation occurs at this point with the bulky nature of the ester group effecting the conformation of the oxaphospholane ring. The conformational change results in an alternate rearrangement of the oxaphospholane to yield the two new cyclopropanes.

The formation of intermediates **A** and **B** in a side reaction along the cyclopropanation pathway and their structure determination aided significantly the elucidation of the mechanism of cyclopropane formation. Although their presence was not necessary for cyclopropanation as shown by the reaction of 1,2-dioxine (**56a**) with ylide (**55d**) the isolation of intermediate **A** and **B** provided a valuable mechanistic tool. Utilising intermediates **A** and **B** in conjunction with D₂O, temperature variations and decomposition with silica as mechanistic probes the secondary cyclopropanation mechanism was elucidated.

Unlike the primary cyclopropanation the formation of cyclopropanes through the secondary manifold was marginally effected by the presence of water. This was partially due to the instability of ylide (**55h**) in water, however, primarily due to hydrolytic deprotonation of the oxaphospholane ring which disfavors quenching of the enolate. In this way the formation of cyclopropanes from the primary manifold were favoured.

The use of deuterated cyclopropanes synthesised through cyclopropanation in the presence of D₂O as discussed in Chapter 4 could enable the synthesis of valuable tools for probing enzyme mechanisms and biosynthetic pathways.

Through manipulation of the reaction conditions it was possible to enhance the yield of cyclopropane (**119**) until it became the predominant cyclopropane thus increasing the reactions potential as a synthetic tool.

Not only did elucidation of intermediates **A** and **B** enable rationalisation of the secondary reaction manifold, it also provided significant support for the original cyclopropanation mechanism, given that both mechanisms proceed through the same initial oxaphospholane intermediate.

Chapter 6: Towards Optically-Enriched Cyclopropanes

Introduction

As stated in Chapter 1, necessity of enantiomeric purity in the synthesis of cyclopropanes is paramount. This is due to the stringent stereochemical requirements of biological systems.

There are three conceivable methods for the creation of enantiomerically-pure cyclopropanes via the two cyclopropanation reactions described in the previous Chapters. The first method requires the employment of standard procedures for resolution of racemic mixtures of cyclopropanes as discussed in Chapter 1.³² This involves chemical attachment of chiral resolving reagents such as amines, acids, alcohols or aldehydes to the racemic cyclopropane, thereby, creating cyclopropyl diastereomers. Separation of the resulting two diastereomers can then be accomplished through recrystallisation or chromatography.

More specifically for use in resolving the cyclopropanes discussed within this thesis, the cyclopropanes could readily be converted into their corresponding acids by hydrolysis of their esters, Chapter 7. Once the cyclopropyl acid is obtained, conversion to its acid corresponding chloride followed by formation of an ester with a chiral alcohol, such as (-)-*N*-methylephedrine would lead to the formation of diastereomers. Subsequent separation of the resultant diastereomers by recrystallisation or chromatography, would enable the cyclopropane enantiomers to be obtained, as discussed in Chapter 1.^{32,33}

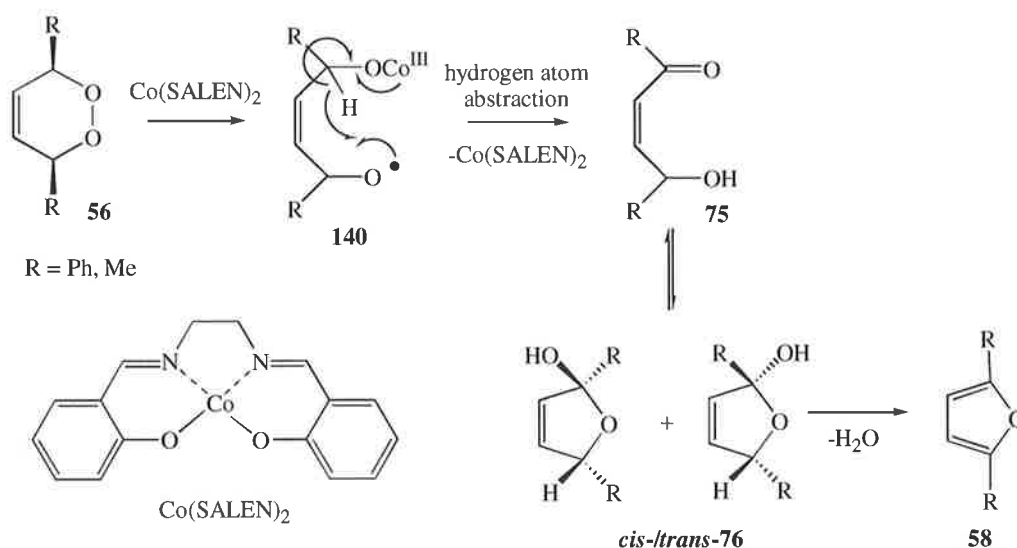
The second method has already been successfully implemented by Palmer *et al.* through the synthesis of enantiomerically-pure *trans* γ -hydroxy enones.⁹² These are allowed to rearrange under photolytic conditions to generate enantiomerically-pure *cis* γ -hydroxy

enones. Reaction with ylides of the type discussed within this thesis allows for the formation of enantiomerically-pure cyclopropanes.

This later method gives precedence to the third method, which is the employment of chiral cobalt catalysts to generate enantiomerically pure *cis* γ -hydroxy enones, directly from prochiral 1,2-dioxines. Reaction with ylide will then yield enantiomerically-pure cyclopropanes. The third method is the method that will be investigated and discussed within this chapter.

Cobalt catalysis utilising $\text{Co}(\text{SALEN})_2$ has already been utilised to rearrange 1,2-dioxines (**56a**) and (**56e**) into *cis* γ -hydroxy enones. The rearrangement was proposed to proceed through cleavage of the peroxide bond via an electron transfer process to generate cobalt complex (**140**). Cleavage of the peroxide bond, is followed by an intramolecular hydrogen atom abstraction process, which results in the formation of a *cis* γ -hydroxy enone species, Scheme 81.

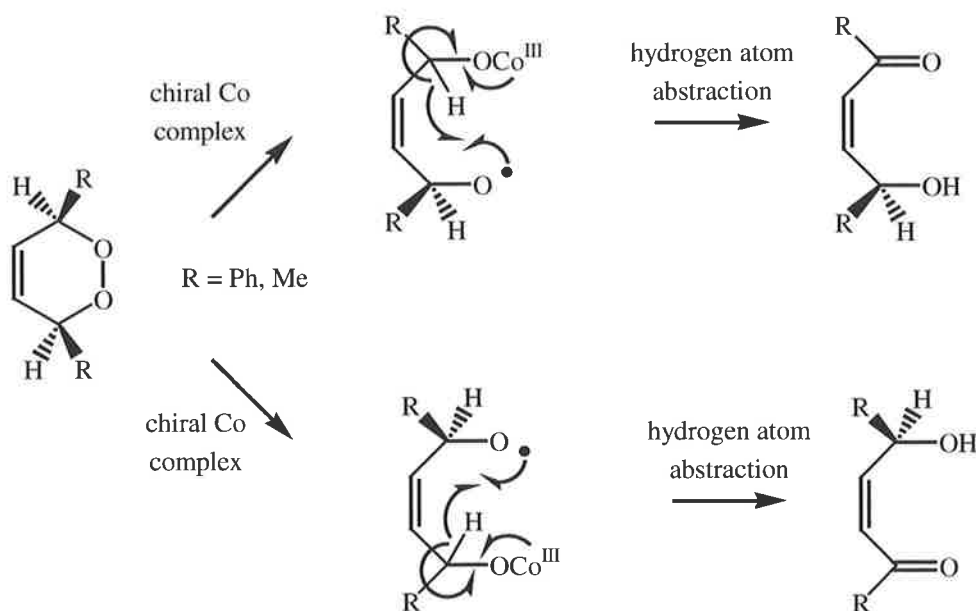
Scheme 81



It has been previously recognised that asymmetric induction via the use of chiral metal-catalysts depends upon the steric environment in which the metal centre exists.¹³⁴ Therefore, given the current mechanism, asymmetric induction was “expected” to occur in the initial complexing of the cobalt catalyst to the 1,2-dioxine through steric interactions, Scheme 82. In this way the catalyst will be arranged to favour “attack” upon

one or the other oxygen atoms of the peroxide bond. Once the cobalt complexes have been formed, intramolecular hydrogen abstraction occurs to generate the enantiomerically-enriched *cis* γ -hydroxy enone. Asymmetric induction via this mechanism requires that the cobalt catalyst remains complexed until after the hydrogen abstraction process.

Scheme 82



Steric interactions of chiral cobalt complex and 1,2-dioxine will favour the formation of one *cis* γ -hydroxy enone over the other.

Due to the regiochemical difficulties encountered when utilising $\text{Co}(\text{SALEN})_2$ to effect the rearrangement of unsymmetrical 1,2-dioxines, this preliminary study was limited to the use of symmetrical 1,2-dioxines.

Results and Discussion

In keeping with the same molecular structure several potential asymmetric catalysts were identified, Figure 13. (*S,S*)-(+)- and (*R,R*)-(-)-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) or (*S,S*)-Jacobsen (**141**) and (*R,R*)-Jacobsen (**142**) respectively were commercially available.¹³⁵ Two other known catalysts (**143**)¹³⁶ and

(**144**)¹³⁷ were chosen to assess the effect of variations in steric bulk and changes in the chiral bridge of the ligands on the induced enantiomeric excess.

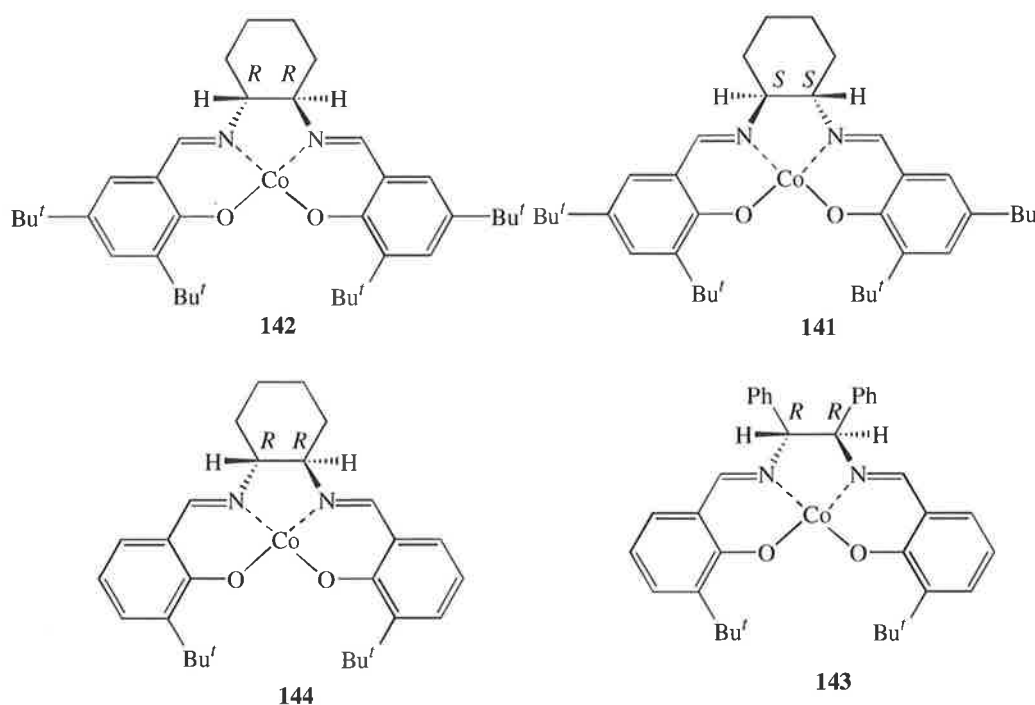
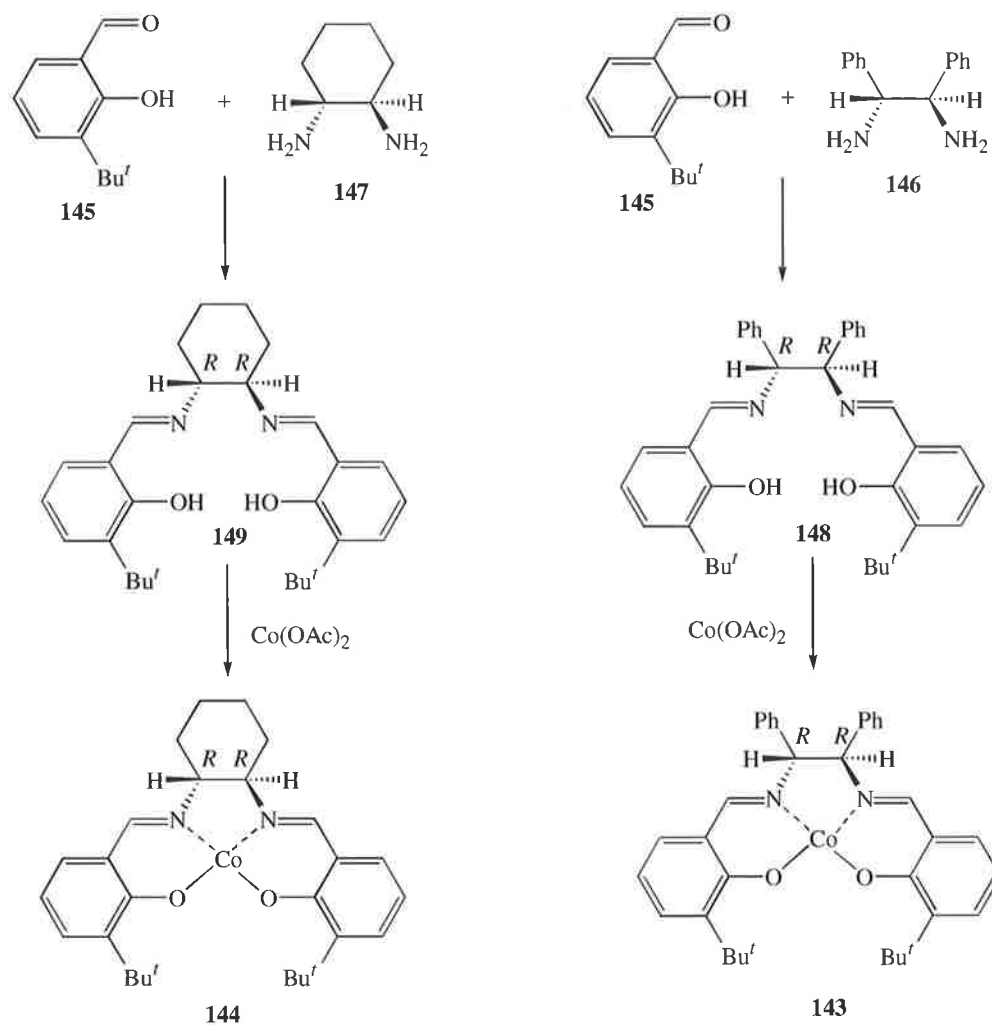


Figure 13. Chiral cobalt catalysts

Cobalt complexes (**143**) and (**144**) were prepared via the general procedure outlined by Fukuda *et al.*¹³⁶ This consisted of the synthesis of the chiral ligand through the coupling of commercially available aldehyde (**145**) and di-amines (**146**) and (**147**) to generate ligands (**148**) and (**149**) respectively. Incorporation of cobalt into the ligands was achieved through treatment of the ligand with cobalt acetate, Scheme 83.¹³⁶

Scheme 83



Determination of enantiomeric excess was carried out through the use of a chiral lanthanide shift (CLS) reagent. This type of experiment was carried out by ^1H NMR analysis of the desired compound in the presence of the CLS reagent. CLS reagents provide a method for determination of enantiomeric excess, through the formation of diastereomeric association complexes with the enantiomers in question.¹³⁸⁻¹⁴¹ These diastereomeric complexes exhibit different ^1H NMR signal due to the inequivalent environments of the two enantiomers in the complexes. The difference in the ^1H NMR signals of the diastereomers is dependant upon and increases with the proportion of CLS reagent. Increasing CLS reagent also results in an increase in the line broadening and increasingly down field chemical shifts of the proton resonances. A compromise, resulting in maximum separation of the ^1H NMR signals of each diastereomeric complex

is, thus, required to ensure accurate peak area determination, as peak area is proportional to the amount of each enantiomer in solution.

In practice 0.5 molar equivalents of the CLS reagent was added initially, with successive additions of 0.5 molar equivalents until maximum separation was observed. The corresponding peak areas of the enantiomers were then measured to obtain the ratio of enantiomers.

The results of the experiments utilising chiral cobalt catalysts to introduce enantiomeric excess into the cyclopropanation reaction manifold are summarised in Table 12. In all reactions the 1,2-dioxines (**56a**) and (**56f**)¹⁴² were fully rearranged to give the *cis* γ -hydroxy enones prior to the addition of ylide to ensure no catalysation from the ylide.

Scheme 84

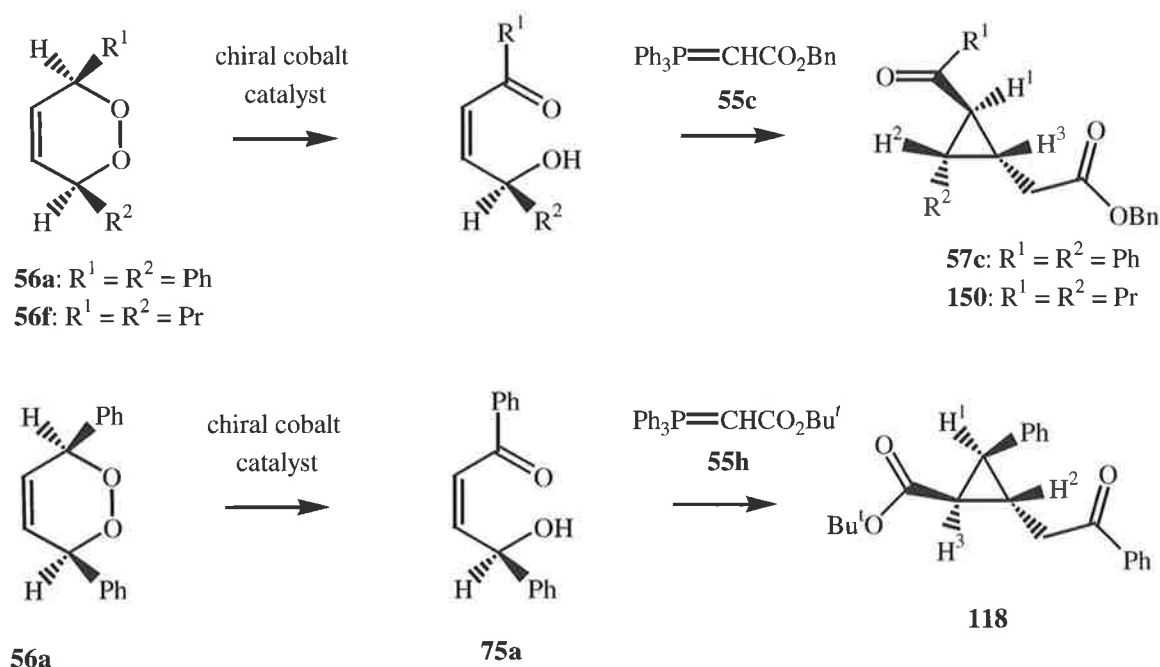


Table 12. The Effect of Various Chiral Cobalt Catalysts on the Formation of Enantiomerically-Enriched Cyclopropanes.^a

entry	catalyst ^b	1,2-dioxine	ylide	cyclopropane ^c	%ee	ratio of enantiomers
1	Co(SALEN) ₂	56a	55c	57c	0	50 : 50; (0)
2	(<i>R,R</i>)-Jacobsen	56a	55c	57c	16	42 : 58; (16)
3	(<i>S,S</i>)-Jacobsen	56a	55c	57c	16	58 : 42; (16)
4 ^d	(<i>S,S</i>)-Jacobsen	56a	55c	57c	18	59 : 41; (18)
5 ^e	(<i>S,S</i>)-Jacobsen	56a	55c	57c	22	61 : 39; (22)
6	(144)	56a	55c	57c	38	31 : 69; (38)
7	(143)	56a	55c	57c	28	36 : 64; (28)
8	(<i>S,S</i>)-Jacobsen	56a	55h	118	16	58 : 42; (16)
9	Co(SALEN) ₂	56f	55c	150	0	50 : 50; (0)
10	(144)	56f	55c	150	28	36 : 64; (28)
11	(143)	56f	55c	150	18	41 : 59; (18)
12	(<i>S,S</i>)-Jacobsen	56f	55c	150	26	63 : 37; (26)

^a All reactions were performed in CH₂Cl₂ under identical concentrations at ambient temperature unless otherwise stated. Reactions were analysed by ¹H NMR (300 or 600 MHz) and ee determined by CLS reagent (¹H NMR analysis). ^b The concentration of each catalyst was 2 mol.% unless otherwise stated. ^c Ee determination was performed on unrecrystallised cyclopropanes to avoid ee enhancement. ^d Reaction carried out in the presence of 10 mol.% catalyst. ^e Reaction carried out at -78 °C.

Initially a control reaction was performed, in which 1,2-dioxine (**56a**) was rearranged with Co(SALEN)₂ and allowed to react with ylide (**55c**) to generate cyclopropane (**57c**), entry 1, Table 12. Analysis with CLS reagent, europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate, in a solution of CCl₄ and benzene-*d*₆ (4 : 1)¹⁴³ revealed, a 50 : 50 % ratio for the two cyclopropyl enantiomers by comparison of the benzyl CH₂ protons signal at approximately δ 6.3 ppm indicating an enantiomeric excess of 0%.

Use of the commercially available Jacobsen's catalyst on 1,2-dioxine (**56a**) resulted in an extremely rapid rate of rearrangement of the 1,2-dioxine (**56a**) to *cis* γ-hydroxy enone (**75a**). An interesting feature of this rearrangement was that it was faster than the establishment of the equilibration of *cis* γ-hydroxy enone (**75a**) with its cyclic hemiacetals (*cis*-/*trans*-**76a**). Therefore, when observed by ¹H NMR a pre-equilibrium formation of

the *cis* γ -hydroxy enone (**75a**) occurred, which proceeded to equilibrate with its cyclic hemiacetals over 5 minutes.

(*R,R*)-Jacobsen catalyst enabled the incorporation of 16% ee into the cyclopropyl product of 1,2-dioxine (**56a**) and ylide (**55c**) entry 2, Table 12. The opposite (*S,S*)-Jacobsen catalyst gave an equal and opposite enantiomeric ratio, entry 3. Upon performing the reaction with increased amounts of catalyst very little increase in the ee was observed, entry 4. A small increase, however, was observed with performance of the reaction at -78 °C, entry 5.

(*R,R*)-Jacobsen catalyst when used in the reaction of 1,2-dioxine (**56a**) and bulky ylide (**55h**), generated an ee of 16% in cyclopropane (**118**) from the secondary cyclopropanation manifold, entry 8. This indicates that the enantiomeric induction is occurring in the *cis* γ -hydroxy enone prior to cyclopropanation and is, therefore, independent of ylide structure. The ee for cyclopropane (**118**) was determined by comparison of the *t*-butyl ester protons signal at approximately δ 2.8 ppm.

The use of catalyst (**144**) resulted in an increase in the ee over that of the Jacobsen catalyst in reactions with both 1,2-dioxine (**56a**) and (**56f**). Use of catalyst (**143**) on 1,2-dioxines (**56a**) and (**56f**) generated ee in the same range as the Jacobsen catalyst. These results indicate that removal of the *t*-butyl group in the external position on the catalysts is beneficial to increasing the ee induction and that the cyclohexyl bridging group enables enhanced ee induction over the corresponding diphenyl bridge.

The reason for the low incorporation of enantiomeric excess within the cyclopropanes could be the result of the cobalt catalyst allowing hydrogen atom abstraction to occur from either oxygen, in other words, the cobalt catalyst may not remain fixed to the *cis* γ -hydroxy enone. On the other hand the steric interaction of the catalysts may not be selective enough, in terms of which face of the 1,2-dioxine is selected, to preclude formation of the opposite enantiomer.

These preliminary experiments lay the foundation for further research into various other chiral Co(SALEN)₂ derivatives.

Summary and Conclusion

Investigations in this chapter have shown that it is possible to induce enantiomeric excess into the primary and secondary cyclopropane manifolds via asymmetric catalysis of 1,2-dioxines to *cis* γ -hydroxy enone with chiral Co(II)-salen complexes. This research may also lead to catalysts which are regioselective as well as enantioselective given the method is currently limited to symmetrical 1,2-dioxines (Chapter 3).

As a consequence of this method it would also be possible to synthesise enantiomerically enriched *trans* γ -hydroxy enones in high yield from symmetrical 1,2-dioxines.

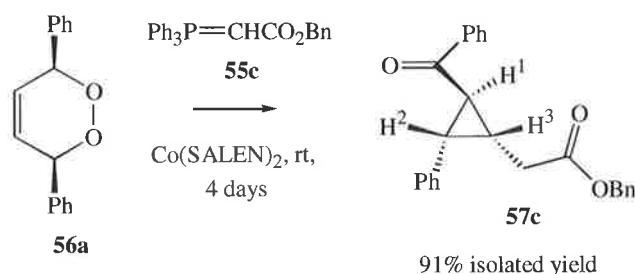
Chapter 7: Closely Related Cyclopropyl Acids

Introduction

As stated previously, the stringent stereochemical requirements of biological receptors requires, that any successful methodology used to synthesise potentially useful compounds should also enable the synthesis of closely related stereoisomers. In this way, the effects that stereochemical changes to structure, within isomers, on biochemical outcomes can be assessed.

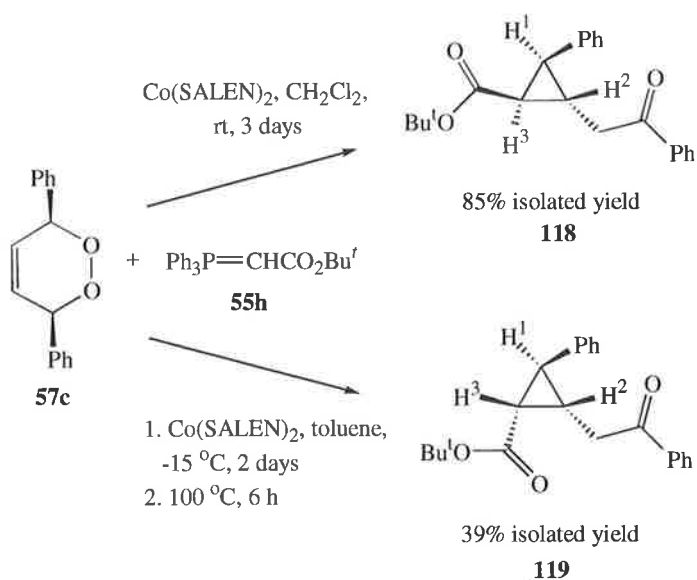
Through the use of stabilised phosphorus ylides and 1,2-dioxines it has been shown that a range of cyclopropyl isomers can be synthesised in high de. As discussed within Chapters 1-4, cyclopropanes of type (**57c**) can be synthesised in high yield and high de, Scheme 85.

Scheme 85



Two further cyclopropyl isomers can be synthesised via the use of the bulky *t*-butyl ester ylide (**55h**), Scheme 86. The diastereomeric ratio of the cyclopropanes (**118**) and (**119**) was able to be manipulated through the use of temperature, as demonstrated in Chapter 5, consequently making both cyclopropyl isomers available for further synthetic transformations.

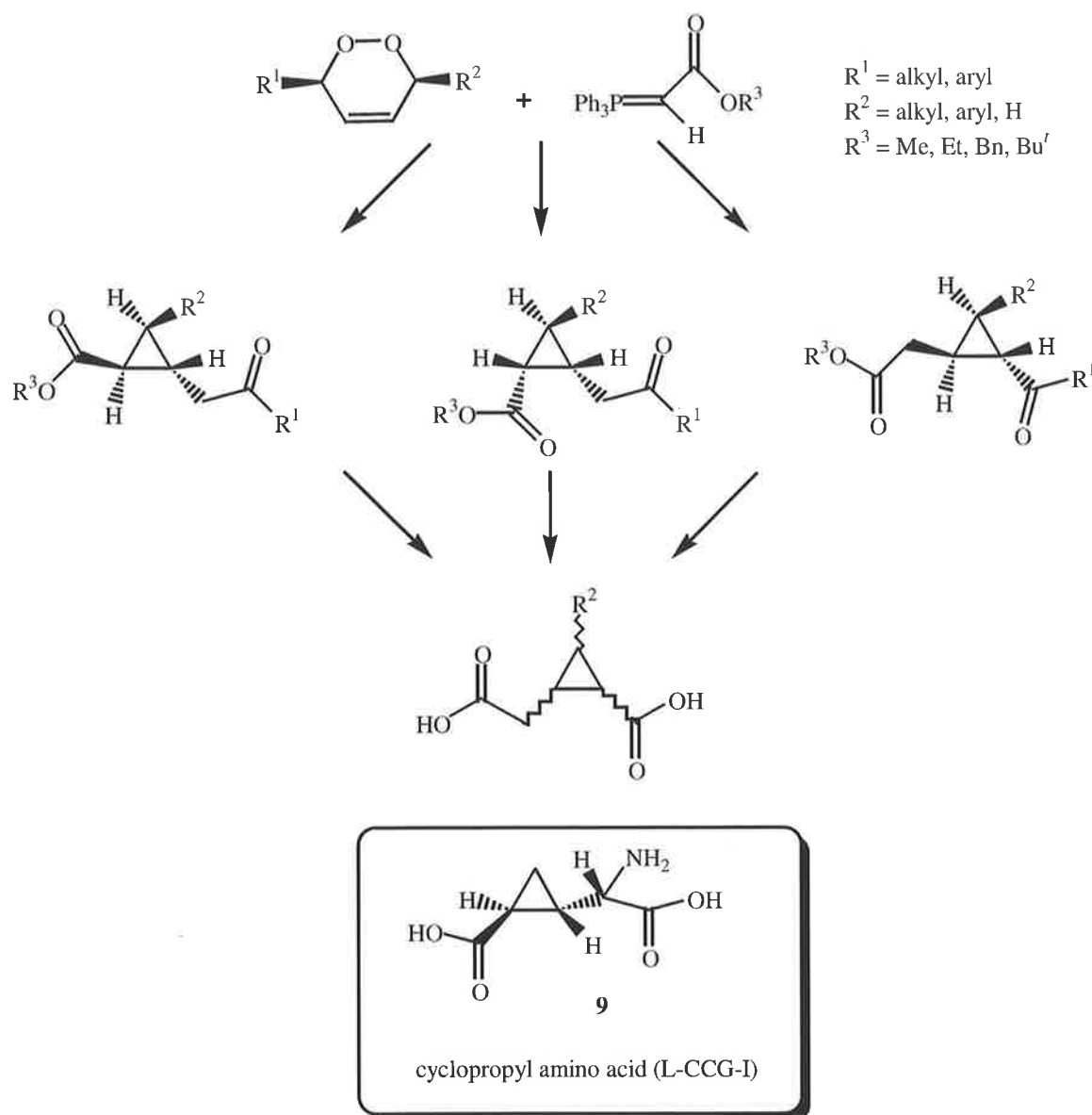
Scheme 86



Therefore, to improve the synthetic utility, relating these cyclopropanes to a single isomeric and synthetically useful precursor can be achieved through simple Baeyer-Villiger, acid- and base-hydrolysis reactions, Scheme 87.

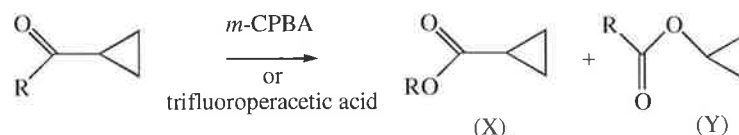
The closely related cyclopropyl di-acids proposed within Scheme 87 could potentially find application in the synthesis of cyclopropyl amino acids of the same structural type as (2*S*,1'*S*,2'*S*)-2-(carboxycyclopropyl)glycine (L-CCG-I) (**9**), Scheme 80, also discussed within Chapter 1.

Scheme 87



Previously a study by Sauers *et al.* was performed on a range of cyclopropyl ketones to establish an order of substituent migration and to correlate this with the previous literature data.¹⁴⁴ Research revealed that phenyl and isopropyl groups show the greatest preference for migration over the cyclopropyl ring in ketones directly attached to the cyclopropyl ring. This was followed by ethyl and methyl ketones, with the methyl substituent showing very little preference over migration of the cyclopropyl group, Scheme 88. The research also demonstrated that the ratio of migration was independent of the peracid used to perform the Baeyer-Villiger reaction.

Scheme 88



R=	<i>m</i> -CPBA		trifluoroperacetic acid	
	X%	Y%	X%	Y%
Me	5	95	4	96
Et	-	-	79	21
Pr ⁱ	99	1	94	6
Ph	97	3	97	3

For creation of the desired cyclopropyl esters, from cyclopropanes of the primary and secondary cyclopropanations, migration of the groups adjacent the cyclopropyl ring are required in order to generate the cyclopropyl carboxylic acids represented in Scheme 87.

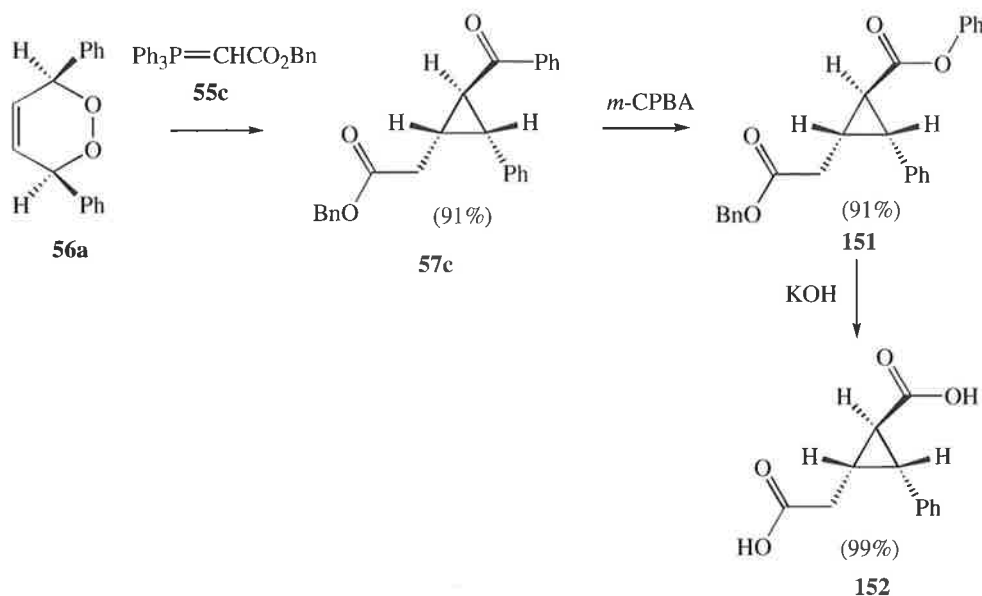
Base hydrolysis of the resulting esters have previously been shown to proceed, without rearrangement or decomposition, to their corresponding cyclopropyl acids.⁸⁰ Given that phenyl migration is favoured over most other substituents it was expected that synthesis of the desired di-acids would proceed in high yield.

Results and Discussion

Cyclopropane (**57c**) was chosen as representative of the primary cyclopropanation and was obtained from the reaction of 1,2-dioxine (**56a**) and benzyl ester ylide (**55c**) in 91% isolated yield. This compound was treated with *m*-CPBA according to the procedure outlined by Sauers *et al.*¹⁴⁴ After two weeks the reaction was worked up and found to be 50% complete. It was also discovered that column chromatography was ineffective in providing sufficient separation of the two cyclopropanes. Therefore, the reaction was set up again with *m*-CPBA and allowed to react for a further two weeks, after which time the reaction had proceeded to completion. ¹H NMR analysis revealed only the desired

Baeyer-Villiger product (**151**), which was isolated in 91% yield. Subsequent basic hydrolysis gave the required cyclopropyl di-acid (**152**) in 99% yield, Scheme 89.

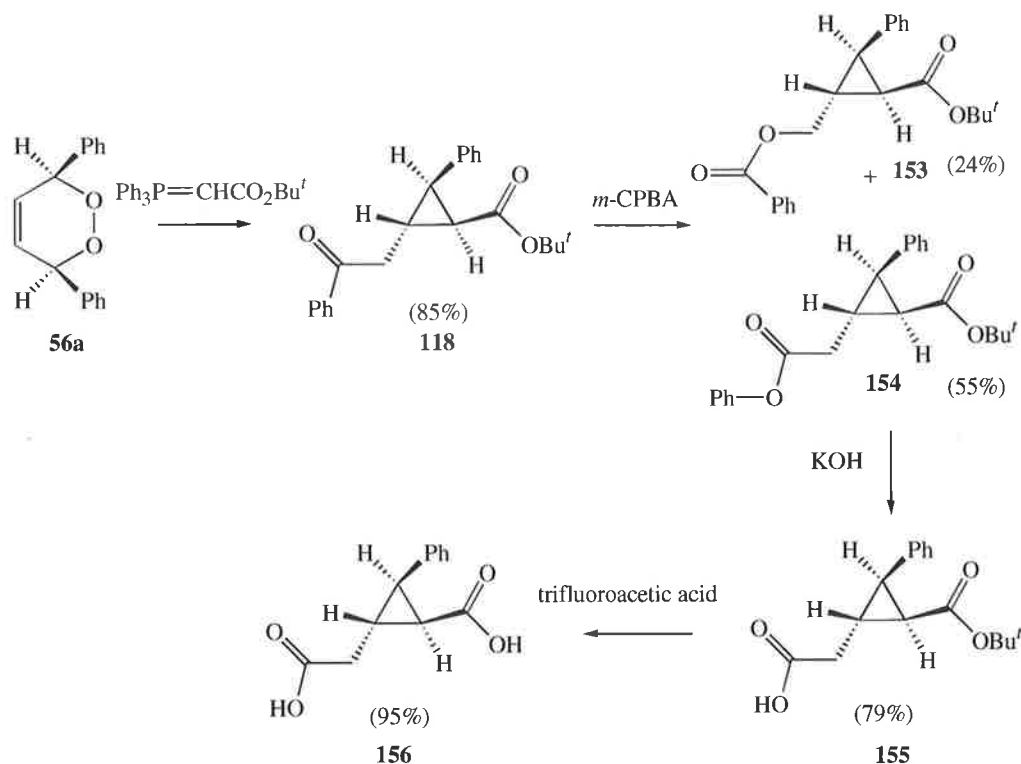
Scheme 89



Conservation of stereochemistry was achieved throughout the course of the synthesis and was and was incontestably proven by X-ray crystallography (Appendix 3).

Cyclopropane (**118**) generated by reaction of 1,2-dioxine (**56a**) and *t*-butyl ester ylide (**55h**) in 85% isolated yield was utilised to synthesis the next of the isomeric cyclopropyl di-acids. Treatment once again under the conditions stipulated by Sauer *et al.* resulted in the formation of two cyclopropyl products, (**153**) and the desired (**154**) in 24% and 55% yield respectively. Basic hydrolysis of the desired di-ester (**154**) resulted in the formation of cyclopropyl mono-acid (**155**) (79% yield), due to the stability of the *t*-butyl ester to basic hydrolysis. Hydrolysis of the *t*-butyl ester was achieved through treatment of the cyclopropyl mono-acid (**155**) with a solution of trifluoroacetic acid.¹⁴⁵ The desired di-acid (**156**) was obtained in 95% yield, Scheme 90.

Scheme 90

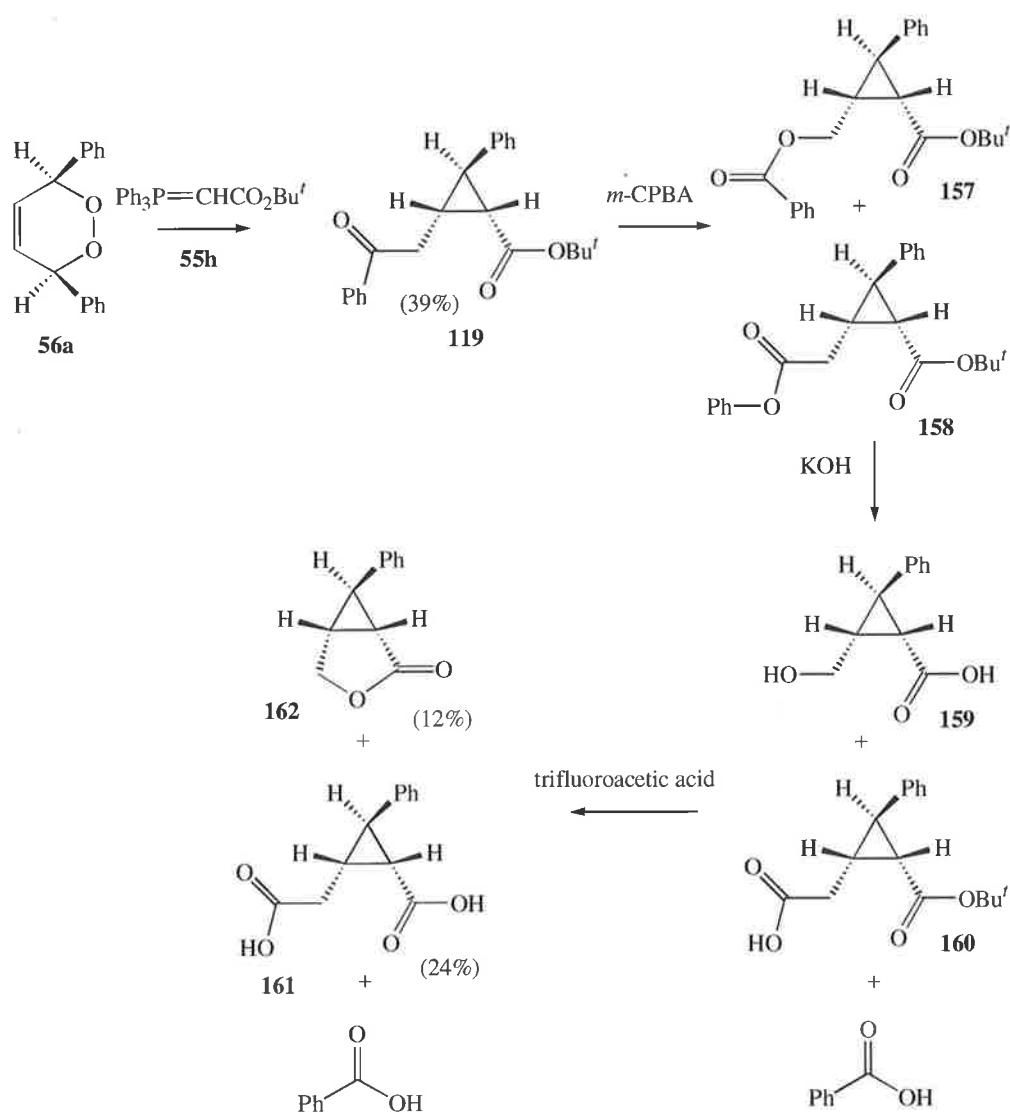


The final cyclopropyl di-acid in the series was derived from cyclopropane (**119**). The yield of cyclopropane (**119**) was maximised using the procedure described in Chapter 5 to obtain 39% isolated yield. Treatment of cyclopropane (**119**) under the Baeyer-Villiger conditions described by Sauer *et al.* resulted in the formation of di-ester (**157**) and desired di-ester (**158**) in a ratio of 1 : 2 respectively. The isomers were inseparable by repetitive column chromatography so an alternate system of resolution was required, Scheme 91.

Basic hydrolysis of the mixture resulted in the formation of mono-acids (**159**) and (**160**) with benzoic acid as an impurity. The unexpected hydrolysis of the *t*-butyl ester functionality producing mono-acid (**159**) was probably due to anchomeric assistance from the neighbouring OH group.⁶³ Separation of the acids at this stage could not be achieved so the mixture of acids was treated with a solution of trifluoroacetic acid. The products resulting from this reaction was the desired di-acid (**161**) and cyclopropyl lactone (**162**) as well as the benzoic acid impurity. Cyclopropyl lactone (**162**) was separated from the di-acid (**161**) and benzoic acid by extraction. The benzoic acid was then removed from the di-acid (**161**) by sublimation to yield the pure di-acid in an overall yield of 24% from

cyclopropane (**119**). Stereochemical stability of the cyclopropanes under the reaction conditions was again demonstrated by X-ray crystallography of the cyclopropyl lactone (**162**) (Appendix 3).

Scheme 91



Summary and Conclusions

Successful synthesis of three closely related stereochemical isomers of the same cyclopropyl di-acid was achieved. This coupled with the potential for high enantiomeric induction in the manifold makes cyclopropanation from 1,2-dioxines and stabilised phosphorus ylides a powerful technique. Also the selective hydrolysis of di-ester (**154**) introduces a synthetically useful tool for the synthesis of other natural products such as the aforementioned cyclopropyl amino acid (L-CCG-I) (**9**).

Experimental Section:

General Methods

Solvents were dried by appropriate methods wherever needed.¹⁴⁶ All organic extracts were dried over anhydrous magnesium sulphate.

All compounds were purified by column chromatography utilising Merck silica gel (230-400 mesh ASTM), unless otherwise stated. Thin-layer chromatography (TLC) was performed upon aluminum sheets of silica gel 60 F₂₅₄ (40 x 80 mm) from Merck. Visualisation under UV 253 nm or by staining using vanillin dip.¹⁴⁷

Melting points were taken on a Reichert Thermovar Kofler apparatus and are uncorrected.

Infrared spectra were recorded on an ATI Mattson Genesis Series FTIR spectrophotometer as nujol mulls unless otherwise stated.

Microanalyses were carried out at the University of Otago, New Zealand.

Accurate mass determination was performed by Dr. Noel Davies, University of Tasmania, Australia. Mass spectra were carried out on a Vacuum Generator ZAB 2HF mass spectrometer operating at 70 eV, via electron impact techniques.

X-ray crystallography of compounds (**64**), (**74**), (**66c**), (**67c**), (**68c**), (**152**), (**162**) was performed on Rigaliu AFC7R by Dr. E. R. T. Tiekink, Adelaide University, South Australia. X-ray crystallography of compounds (**118**), (**119**), (**125**) and (**120**) was performed on GDF: Nonius CCD by Dr. G. D. Fallon, Monash University, Victoria.

¹H and ¹³C NMR spectra were recorded in CDCl₃ solutions on either a Varian Gemini 2000 (300 MHz) or Varian INOVA (600 MHz) instrument, TMS (0 ppm) and CDCl₃

(77.0 ppm) were used as internal standards unless otherwise stated. ^{31}P NMR chemical shifts referenced to 85% aqueous H_3PO_4 (external) in CDCl_3 with a negative shift indicating an upfield shift. ABX spectra were analysed by use of the effective Larmor frequencies method.¹⁴⁸ The correct analytical solution was then confirmed by spectral synthesis using VNMR 6.1B (Varian Inc., Palo Alto, CA).

All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy.

The following compounds were purchased from Aldrich Chemical Company, Inc. and used without further purification. Triphenylalkydenephosphoranes (**55a-h**), 4-(trifluoromethyl)benzyl bromide (**94c**), *N,N'*-bis(salicylidene)-ethylenediaminocobalt(II), *N,N'*-bis(salicylidene)-ethylenediaminocobalt(II) hydrate, (*S,S*)-(+)-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II), (*R,R*)-(-)-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II), 3-*tert*-butyl-2-hydroxybenzaldehyde, (1*R*,2*R*)-(-)-1,2-diaminocyclohexane, (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine, *trans*-styrylacetic acid, *trans,trans*-1,4-diphenyl-1,3-butadiene, Rose Bengal, bis(triethylammonium)salt, 2,3-dihydrofuran, europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

Compounds Described in Chapter 2

General procedure for the preparation of triphenyl phosphonium halides (**94a-d**).

To a solution of triphenylphosphine (12 g, 46 mmol) in anhydrous toluene (56 mL), was added benzyl bromide (10 g, 58 mmol), dropwise over 10 minutes. The solution was stirred under an atmosphere of nitrogen for 48 h, after which time vacuum filtration gave the crude product. The solid was then washed with toluene (100 mL), refiltered and dried to yield **benzyl(triphenyl)phosphonium bromide (95a)** (17.0 g, 85%).¹⁴⁹ All examples were carried out under the standard conditions described above.

Methyl(triphenyl)phosphonium bromide (95b).¹⁰³ Yield 97.4 g, 97%.

***p*-(Trifluoromethyl)benzyltriphenylphosphonium bromide (95c).**¹⁴⁹ Yield 20.4 g, 81%.

Ethyl(triphenyl)phosphonium iodide (95d).¹⁰³ Yield 45.3 g, 84%.

General procedure for the preparation of 1,3-butadienes (97b-e). To a suspension of vigorously stirred benzyl triphenylphosphine bromide (**95a**) (21.7 g, 46 mmol) in ether (200 mL) at 0 °C, was added potassium *tert*-butoxide (7.8 g, 70 mmol) under an atmosphere of nitrogen. The mixture was stirred for 30 minutes, after which time *trans*-crotonaldehyde (**96b**) (4 mL, 50 mmol) was added dropwise over 10 minutes. Subsequent stirring for 24 hours and column chromatography yielded a (1 : 1) mixture of **1-[(1E,3Z)-1,3-Pentadienyl]benzene : 1-[(1E,3E)-1,3-Pentadienyl]benzene (97b)**¹⁵⁰ (7.1 g, 99%). All examples were carried out under the standard conditions described above.

1-[(1E)-1,3-Butadienyl]benzene (97c).¹⁵⁰ Yield 10.2 g, 99%, synthesised from the action of methyl(triphenyl)phosphonium bromide (**95b**) on *trans*-cinnamaldehyde (**96a**).

1-[(1E,3E)-1,3-Pentadienyl]-4-(trifluoromethyl)benzene : 1-[(1Z,3E)-1,3-Pentadienyl]-4-(trifluoromethyl)benzene (97d). Yield 5.7 g, 96%, synthesised in a 1 : 1 ratio of isomers, from the action of *p*-(trifluoromethyl)benzyltriphenylphosphonium bromide (**95c**) on *trans*-crotonaldehyde (**96b**). **(1E,3E) (97d).** *R_f* 0.75 (hexane); IR (neat) 1679, 1643, 1614, 1575 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.82 (dd, *J* = 6.9, 1.5 Hz, 3H), 5.89 (dq, *J* = 15.0, 6.9 Hz, 1H), 6.21 (ddq, *J* = 15.0, 10.2, 1.5 Hz, 1H), 6.40 (d, *J* = 15.5 Hz, 1H), 6.80 (dd, *J* = 15.5, 10.2 Hz, 1H), 7.40-7.43 (m, 2H), 7.50-7.53 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 18.3, 124.3 (q, *J* = 270 Hz), 125.4 (q, *J* = 4.0 Hz), 126.1, 128.1, 128.7 (q, *J* = 33 Hz), 131.5, 131.8, 132.3, 141.2. **(1Z,3E) (97d).** *R_f* 0.80 (hexane); IR (neat) 1687, 1644, 1614, 1577 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.80 (dd, *J* = 7.2, 1.8 Hz, 3H), 5.93 (dq, *J* = 15.0, 7.2 Hz, 1H), 6.24-6.33 (m, 2H), 6.55 (ddq, *J* = 15.0, 10.2, 1.8 Hz, 1H), 7.38-7.41 (m, 2H), 7.56-7.59 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 18.3, 124.3 (q, *J* = 270 Hz), 125.1 (q, *J* = 4.0 Hz), 125.7, 127.3, 128.6 (q, *J* = 33 Hz), 129.0, 132.4, 134.2, 141.5; MS *m/z* (%): 212 (25), 151 (76), 131 (100), 103 (52). The titled 1,3-butadienes(**97d**) were found to slowly polymerise at ambient temperature.

(2E,4E)-2,4-Hexadiene : (2E,4Z)-2,4-Hexadiene (97e).¹⁵¹ Yield 5.7 g, 95%, synthesised in a 1 : 2 ratio of isomers, from the action of ethyl(triphenyl)phosphonium iodide (**94d**) on *trans*-crotonaldehyde (**96b**).

General procedure for the preparation of 1,2-dioxines (56a-e). 1,3-butadiene (3 g) and Rose bengal, bis(triethylammonium)salt (100 mg) were dissolved in dry dichloromethane (100 mL). Ice water was pumped through the reaction vessel so as to maintain a temperature of approximately 5-10 °C within the reaction mixture at all times. Oxygen was then passed through the solution, whilst irradiating with three tungsten halogen lamps (500 W) at a distance of 10 cm from the reaction vessel for approximately 6 hours. The volatiles were then removed *in vacuo* and the residue subjected to column chromatography. All examples were carried out under the standard conditions described above. All 1,2-dioxines were stored at 4 °C without decomposition.

3,6-Diphenyl-3,6-dihydro-1,2-dioxine (56a). Yield 3.2 g, 97%; R_f 0.50 (9 : 1 hexane / ethyl acetate); Mp: 89.5-90.5 °C (hexane). (Lit.¹⁵² Mp: 83.5-84 °C).

3-Methyl-6-phenyl-3,6-dihydro-1,2-dioxine (56b).¹⁵² Yield 2.8 g, 77%; R_f 0.50 (9 : 1 hexane / ethyl acetate).

3-Phenyl-3,6-dihydro-1,2-dioxine (56c).¹⁵² Yield 1.1 g, 30%; R_f 0.60 (9 : 1 hexane / ethyl acetate).

3-Methyl-6-[4-(trifluoromethyl)phenyl]-3,6-dihydro-1,2-dioxine (56d). Yield 1.0 g, 30%; R_f 0.50 (9 : 1 hexane / ethyl acetate); IR (neat) 2981, 1620, 1417, 1327, 846 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.32 (d, J = 6.6 Hz, 3H), 4.81-4.85 (m, 1H), 5.48 (s, 1H), 6.07-6.13 (m, 2H), 7.52-7.53 (m, 2H), 7.62-7.64 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 18.0, 74.5, 79.0, 124.1 (q, J = 270 Hz), 125.1, 125.4 (q, J = 4.0 Hz), 128.5, 130.6 (q, J = 32 Hz), 142.3; MS m/z (%): 244 (M^+ , 5), 233 (100), 220 (53), 198 (30), 167 (90). The titled 1,2-dioxine (**56d**) was found to slowly polymerise at ambient temperature.

3,6-Dimethyl-3,6-dihydro-1,2-dioxine (56e).¹⁵² Yield 2.1 g, 51%; R_f 0.60 (9 : 1 hexane / ethyl acetate).

General procedure for preparation of *trans* γ -hydroxy enones (77a-d) from 1,2-dioxines (56a-d). To a solution of the 1,2-dioxine (1.2 mmol) in dichloromethane (2 mL) at ambient temperature was added a mixture of triethylamine (1.2 mmol) and triphenylphosphine (0.6 mmol) dissolved in dichloromethane (0.5 mL) was added. The solution was stirred until cessation of reaction (as determined by TLC, approx. 2 hours) after which time the volatiles were removed *in vacuo*, with subsequent column chromatography of the residue, to afford the desired *trans* γ -hydroxy enone. All examples collated in Table 4 were carried out under the standard conditions described above. All *trans* γ -hydroxy enones (77a-d) were found to undergo slow rearrangement into furans (58a-d)

(*E*)-4-Hydroxy-1,4-diphenyl-2-buten-1-one (77a). Yield 234 mg, 82%; R_f 0.50 (2 : 1 hexane / ethyl acetate); IR (CDCl₃) 3419, 1670, 1624, 1599, 1579, 1448 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 2.16 (d, J = 3.9 Hz, exch. D₂O, 1H), 5.50 (ddd, J = 4.4, 3.9, 1.7 Hz, 1H), 7.14 (dd, J = 15.4, 4.4 Hz, 1H), 7.28 (dd, J = 15.4, 1.7 Hz, 1H), 7.32-7.35 (m, 1H), 7.37-7.44 (m, 4H), 7.46-7.50 (m, 2H), 7.55-7.58 (m, 1H), 7.96-7.98 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 74.0, 123.6, 126.7, 128.5, 128.6, 128.6, 128.9, 133.0, 137.6, 140.9, 148.4, 190.5.

(*E*)-4-Hydroxy-1-phenyl-2-penten-1-one (77b). Yield 201 mg, 95%; R_f 0.50 (3 : 2 hexane / ethyl acetate); IR (CDCl₃) 3434, 1668, 1628, 1599, 1579, 1448 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.39 (d, J = 7.2 Hz, 3H), 2.60 (bs, exch. D₂O, 1H), 4.59 (ddq, J = 7.2, 5.3, 1.2 Hz, 1H), 7.05 (dd, J = 15.4, 5.3 Hz, 1H), 7.14 (dd, J = 15.4, 1.2 Hz, 1H), 7.42-7.50 (m, 2H), 7.53-7.58 (m, 1H), 7.92-7.96 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 22.9, 67.5, 123.3, 128.5, 128.6, 132.9, 137.7, 151.2, 190.8.

(*E*)-4-Hydroxy-1-phenyl-2-buten-1-one (77c). Yield 165 mg, 85%; R_f 0.40 (11 : 9 hexane / ethyl acetate); IR (CDCl₃) 3427, 1672, 1628, 1599, 1579, 1448 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.65 (t, J = 5.4 Hz, exch. D₂O, 1H), 4.49 (ddd, J = 5.4, 3.6, 1.8 Hz, 2H), 7.14 (dt, J = 15.0, 3.6 Hz, 1H), 7.23 (dt, J = 15.0, 1.8 Hz, 1H), 7.46-7.51 (m, 2H),

7.56-7.60 (m, 1H), 7.96-8.00 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 62.3, 124.0, 128.6, 128.6, 132.9, 137.7, 146.9, 190.5.

(*E*)-4-Hydroxy-1-[4-(trifluoromethyl)phenyl]-2-penten-1-one (77d). Yield 225mg, 77%; R_f 0.50 (2 : 1 hexane / ethyl acetate); IR (neat) 3429, 1673, 1627, 1580, 1512, 1326, 1013, 837 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.41 (d, J = 6.6 Hz, 3H), 1.96 (bs, exch. D_2O , 1H), 4.64 (dq, J = 6.6, 2.7 Hz, 1H), 7.18-7.23 (m, 2H), 7.72-7.75 (m, 2H), 8.02-8.05 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 22.9, 67.5, 121.8, 123.6(q, J = 271 Hz), 125.6 (q, J = 4.0 Hz), 128.9, 129.7 (q, J = 32 Hz), 136.0, 152.4, 189.8.

Formation of furans (58a-d) from *trans* γ -hydroxy enones (77a-d). *trans* γ -Hydroxy enones (77a-d) were found to be labile undergoing slow thermal rearrangement to give quantitative formation of furans (58a-d). Compounds **2,5-diphenylfuran (58a)**,¹⁵³ **2-methyl-5-phenylfuran (58b)**¹⁵⁴ and **2-phenylfuran (58c)**¹⁵⁴ were identified by comparison with the chemical and physical properties reported for the known compounds.

2-Methyl-5-[4-(trifluoromethyl)phenyl]furan (58d). R_f 0.60 (hexane); Mp: 56-57 $^\circ\text{C}$; ^1H NMR (CDCl_3 , 300 MHz) δ 2.39 (d, J = 2.0 Hz, 3H), 6.10 (dq, J = 6.6, 2.0 Hz, 1H), 6.66 (d, J = 6.6 Hz, 1H), 7.58-7.61 (m, 2H), 7.69-7.72 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 13.6, 108.0, 108.1, 124.3 (q, J = 270 Hz), 125.7 (q, J = 3.8 Hz), 128.4 (q, J = 33 Hz), 134.3, 150.9, 153.3; MS m/z (%): 226 (M^+ , 57), 207 (11), 177 (19), 145 (21), 129 (32), 53 (2), 43 (100); Anal. Calcd for $\text{C}_{12}\text{H}_9\text{F}_3\text{O}$ (226.2): C, 63.72; H, 4.01. Found: C, 64.04; H, 4.16.

Treatment of *trans* γ -hydroxy enone (77a) with *p*-TSA. A solution of *trans* γ -hydroxy enone (77a) (100 mg, 0.42 mmol) in dichloromethane (5 mL) was allowed to react with *p*-TSA monohydrate (10 mg, 0.05 mmol) for 1 hour at ambient temperature. Subsequent removal of the volatiles and column chromatography (R_f 0.8, 19:1 hexane / ethyl acetate) afforded 2,5-diphenylfuran (58a) (90.5 mg, 98%).¹⁵³

General procedure for the reaction of stabilised ylides (55a,c-e) with *trans* γ -hydroxy enones (77a-d). A mixture of *trans* γ -hydroxy enone (77a) (212 mg, 0.89 mmol) was allowed to react with benzyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (55c) (369 mg, 0.9

mmol) in anhydrous dichloromethane (10 mL) under an atmosphere of nitrogen at ambient temperature for 2 weeks. Subsequent removal of the volatiles *in vacuo* afforded the crude cyclopropane (**57a**) (135 mg, 41%) along with 1,4-dicarbonyl (**59a**) (106 mg, 50%). All examples shown in Table 5 were carried out under the standard conditions outlined above. For reaction times and yields refer to Table 5. Column chromatography and subsequent recrystallisation from heptane, where applicable, afforded the pure cyclopropanes. The *cis* / *trans* nomenclature utilised in naming cyclopropanes and their deuterio-analogues, refers to in the *cis* / *trans* orientation of H¹ in relation to H² and H³ of the cyclopropyl ring system, Scheme 20.

***trans* (±) Benzyl 2-(2-benzoyl-3-phenylcyclopropyl)acetate (57c).** *R_f* 0.50 (4 : 1 hexane / ethyl acetate); Mp 89.5-90.5 °C (heptane); IR 1727, 1663, 1598, 1164 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 2.20 (dd, *J* = 16.1, 8.3 Hz, 1H), 2.35 (dddd, *J* = 9.3, 8.3, 6.4, 4.9 Hz, 1H), 2.44 (dd, *J* = 16.1, 6.4 Hz, 1H), 3.10 (dd, *J* = 4.9, 4.9 Hz, 1H), 3.13 (dd, *J* = 9.3, 4.9 Hz, 1H), 5.04 and 5.07 (AB_q, *J* = 12.6 Hz, 2H), 7.21-7.32 (m, 10H), 7.48-7.51 (m, 2H), 7.58-7.62 (m, 1H), 8.04-8.07 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ 27.1, 29.3, 33.1, 33.5, 66.4, 127.1, 128.2, 128.2, 128.3, 128.6, 128.7, 129.0, 133.1, 135.7, 135.9, 137.8, (one aromatic carbon masked), 172.0, 198.7; MS *m/z* (%): 370 (M⁺, 0.1), 279 (100), 221 (15), 105 (83), 91 (52); Anal. Calcd for C₂₅H₂₂O₃ (370.4): C, 81.06; H, 5.99. Found: C, 80.62; H, 5.98.

***trans* (±) Ethyl 2-(2-benzoyl-3-phenylcyclopropyl)propanoate (57d).** Yield 63 mg, 4%; *R_f* 0.55 (4 : 1 hexane / ethyl acetate); Mp 61-62 °C (heptane); IR (neat) 1730, 1668, 1599, 1581, 1450, 1219 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.05 (d, *J* = 6.6 Hz, 3H), 1.10 (t, *J* = 7.0 Hz, 3H), 2.01 (dq, *J* = 10.5, 6.6 Hz, 1H), 2.07 (ddd, *J* = 10.5, 9.0, 5.0 Hz, 1H), 3.16 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.33 (dd, *J* = 5.0, 5.0 Hz, 1H), , 4.04-4.08 (m, AB portion of ABX₃, 2H), 7.22-7.36 (m, 5H), 7.48-7.51 (m, 2H), 7.56-7.59 (m, 1H), 8.06-8.08 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ 14.0, 15.9, 28.7, 33.3, 35.7, 38.2, 60.5, 126.8, 128.1, 128.4, 128.5, 128.5, 132.9, 135.36, 137.7, 175.1, 198.3; MS *m/z* (%): 322 (M⁺, 8), 276 (10), 222 (99), 143 (49), 105 (100); Anal. Calcd for C₂₁H₂₂O₃ (322.4): C, 78.23; H, 6.88. Found: C, 77.98; H, 6.81.

***trans* (±) Benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (66c).** Yield 201 mg, 74%; R_f 0.37 (4 : 1 hexane / ethyl acetate); Mp 54.5-56 °C (heptane); IR 1726, 1659, 1171 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.21 (d, J = 6.6 Hz, 3H), 1.87 (ddq, J = 10.8, 6.6, 4.4 Hz, 1H), 2.08 (dddd, J = 10.8, 7.8, 6.8, 4.4 Hz, 1H), 2.26 (dd, J = 4.4, 4.4 Hz, 1H), 2.52 (dd, J = 16.1, 7.8 Hz, 1H), 2.61 (dd, J = 16.1, 6.8 Hz, 1H), 5.12 (s, 2H), 7.29-7.30 (m, 5H), 7.43-7.46 (m, 2H), 7.53-7.56 (m, 1H), 7.93-7.95 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 12.4, 24.4, 26.3, 32.5, 32.7, 66.4, 127.9, 128.1, 128.2, 128.4, 128.5, 132.6, 135.7, 138.0, 171.9, 199.0; MS m/z (%): 308 (M^+ , 5), 217 (37), 105 (84), 91 (100); Anal. Calcd for $\text{C}_{20}\text{H}_{20}\text{O}_3$ (308.4): C, 77.90; H, 6.54. Found: C, 78.04; H, 6.52.

***cis* (±) Benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (69c).** Yield 27 mg, 10%; R_f 0.42 (4 : 1 hexane / ethyl acetate); IR (neat) 1737, 1664, 1597, 1578, 1448, 1213, 1168 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.21 (d, J = 6.0 Hz, 3H), 1.83 (ddq, J = 8.8, 8.8, 6.0 Hz, 1H), 1.93 (dddd, J = 8.8, 8.8, 7.8, 6.8 Hz, 1H), 2.80 (dd, J = 8.8, 8.8 Hz, 1H), 2.91 (dd, J = 17.6, 6.8 Hz, 1H), 2.99 (dd, J = 17.6, 7.8 Hz, 1H), 5.08 and 5.10 (AB_q, J = 12.6 Hz, 2H), 7.28-7.33 (m, 5H), 7.42-7.46 (m, 2H), 7.53-7.56 (m, 1H), 7.90-7.94 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 7.3, 22.0, 23.1, 24.3, 27.8, 66.1, 127.7, 128.0, 128.4, 128.5, 128.7, 132.3, 136.1, 139.8, 173.1, 199.5.

***trans* (±) Methyl 2-(2-benzoylcyclopropyl)acetate (67a).** Yield 149 mg, 97%; R_f 0.25 (10 : 1 benzene / ethyl acetate); IR (neat) 1738, 1668, 1598, 1578, 1450, 1223, 753, 703 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 0.99 (ddd, J = 8.4, 5.4, 4.8 Hz, 1H), 1.56 (ddd, J = 8.4, 5.4, 4.8 Hz, 1H), 1.88 (dddd, J = 8.4, 7.8, 6.6, 5.4, 4.8 Hz, 1H), 2.36 (dd, J = 15.6, 7.8 Hz, 1H), 2.55 (dd, J = 15.6, 6.6 Hz, 1H), 2.60 (ddd, J = 8.4, 4.8, 4.8 Hz, 1H), 3.68 (s, 3H), 7.46-7.49 (m, 2H), 7.55-7.58 (m, 1H), 8.00-8.02 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 17.6, 21.4, 24.4, 37.9, 51.8, 128.1, 128.5, 132.8, 137.9, 172.2, 199.1; MS m/z (%): 218 (M^+ , 3), 159 (21), 145 (86), 144 (95), 105 (100); HRMS of (67a), $\text{C}_{13}\text{H}_{14}\text{O}_3$: calcd, 218.0943; found, 218.0932.

***trans* (±) Benzyl 2-(2-benzoylcyclopropyl)acetate (67c).** Yield 156 mg, 96%; R_f 0.40 (4 : 1 hexane / ethyl acetate); Mp 44-45 °C (heptane); IR 1723, 1663, 1175 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.00 (ddd, J = 8.5, 6.8, 4.8 Hz, 1H), 1.55 (ddd, J = 8.9, 4.8, 4.8 Hz, 1H), 1.90 (dddd, J = 8.9, 7.8, 6.8, 6.1, 4.8 Hz, 1H), 2.38 (dd, J = 16.0, 7.8 Hz, 1H), 2.59

(ddd, $J = 8.5, 4.8, 4.8$ Hz, 1H), 2.62 (dd, $J = 16.0, 6.1$ Hz, 1H), 5.11 and 5.13 (AB_q, $J = 12.6$ Hz, 2H), 7.28-7.31 (m, 5H), 7.44-7.46 (m, 2H), 7.54-7.57 (m, 1H), 7.96-7.99 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ 17.7, 21.4, 24.3, 38.1, 66.5, 128.1, 128.1, 128.2, 128.5, 128.5, 132.8, 135.7, 137.8, 171.6, 199.1; MS m/z (%): 294 (M⁺, 15), 276 (10), 235 (33), 105 (70), 91 (100); Anal. Calcd for C₁₉H₁₈O₃ (294.4): C, 77.53; H, 6.16. Found: C, 77.73; H, 6.14.

trans (±) Benzyl 2-{2-methyl-3-[4-(trifluoromethyl)benzoyl]cyclopropyl}acetate (68c). Yield 211 mg, 73%; R_f 0.50 (4 : 1 hexane / ethyl acetate); Mp 91-92 °C (heptane); IR 1726, 1666, 1327, 1173 cm⁻¹; ¹H NMR (CDCl₃, 600 MHz) δ 1.23 (d, $J = 6.6$ Hz, 3H), 1.92 (ddq, $J = 9.3, 6.6, 4.2$ Hz, 1H), 2.08 (dddd, $J = 9.3, 8.4, 6.6, 4.2$ Hz, 1H), 2.24 (dd, $J = 4.2, 4.2$ Hz, 1H), 2.49 (dd, $J = 16.2, 8.4$ Hz, 1H), 2.66 (dd, $J = 16.2, 6.6$ Hz, 1H), 5.13 and 5.11 (AB_q, $J = 13.2$ Hz, 2H), 7.26-7.29 (m, 5H), 7.67-7.69 (m, 2H), 8.00-8.02 (m, 2H); ¹³C NMR (CDCl₃, 150 MHz) δ 12.5, 25.1, 27.8, 32.8, 32.9, 66.6, 123.7 (q, $J = 271$ Hz), 125.5 (q, $J = 3.5$ Hz), 128.2, 128.3, 128.3, 128.5, 133.9 (q, $J = 33$ Hz), 135.6, 140.6, 171.9, 198.3; MS m/z (%): 376 (M⁺, 1), 358 (2), 285 (18), 173 (33), 145 (13), 91 (100); Anal. Calcd for C₂₁H₁₉F₃O₃ (376.4): C, 67.02; H, 5.09. Found: C, 66.97; H, 5.11.

cis (±) Benzyl 2-{2-methyl-3-[4-(trifluoromethyl)benzoyl]cyclopropyl}acetate (71c). Yield 35 mg, 12%; R_f 0.55 (4 : 1 hexane / ethyl acetate). The titled compound (**71c**) was found to be unstable at ambient temperature undergoing an enolene rearrangement over several days to afford quantitatively the α,β -unsaturated ester (**72c**).

Benzyl (E)-4-methyl-6-oxo-6-[4-(trifluoromethyl)phenyl]-2-hexenoate (72c). R_f 0.45 (4 : 1 hexane / ethyl acetate); IR (CHCl₃) 1714, 1697, 1655, 1583, 1512, 1456, 1410, 1173, 1066 cm⁻¹; ¹H NMR (600 MHz) δ 1.17 (d, $J = 6.8$ Hz, 3H), 2.98-3.18 (m, 3H), 5.17 (s, 2H), 5.91 (d, $J = 15.7$ Hz, 1H), 7.02 (dd, $J = 15.7, 6.8$ Hz, 1H), 7.30-7.39 (m, 5H), 7.70-7.78 (m, 2H) 8.01-8.07 (m, 2H); ¹³C NMR (150 MHz) δ 19.1, 31.8, 42.9, 66.2, 120.1, 123.7 (q, $J = 274$ Hz), 125.8 (q, $J = 3.9$ Hz), 128.3, 128.3, 128.4, 128.6, 134.5 (q, $J = 33$ Hz), 136.0, 152.8, 171.7, 197.0; MS m/z (%): 376 (M⁺, 0.1), 270 (8), 242 (11), 173 (62), 145 (28), 91 (100), 82 (83); HRMS of (**72c**), C₂₁H₁₉F₃O₃: calcd, 376.1286; found, 376.1274.

Generation of 1,4-dicarbonyls (59a-d) from *trans* γ -hydroxy enones (77a-d). *trans* γ -Hydroxy enones (77a-d) in the presence of ylides (55a,c-e) were found to generate 1,4-dicarbonyls (59a-d), Table (). Compounds **1,4-diphenyl-1,4-butanedione (59a)**,¹¹⁸ **1-phenyl-1,4-pentanedione (59b)**¹⁵⁵ and **4-oxo-4-phenylbutanal (59c)**¹⁵³ were identified by comparison with the chemical and physical properties reported for the known compounds.

1-[4-(Trifluoromethyl)phenyl]-1,4-pentanedione (59d). R_f 0.50 (2 : 1 hexane / ethyl acetate); Mp: 79-80 °C; IR 1708, 1682, 1577, 1134, 845 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 2.25 (s, 3H), 2.91 (t, $J = 5.7$ Hz, 2H), 3.27 (d, $J = 5.7$ Hz, 2H), 7.71-7.74 (m, 2H), 8.06-8.09 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 29.9, 32.6, 36.9, 123.6 (q, $J = 272$ Hz), 125.7 (q, $J = 3.8$ Hz), 128.4, 134.5 (q, $J = 33$ Hz), 139.4, 197.8, 207.0; MS m/z (%): 226 (M^+ , 13), 229 (34), 201 (10), 173 (100), 145 (57), 43 (71); Anal. Calcd for $\text{C}_{12}\text{H}_{11}\text{F}_3\text{O}_2$ (244.2): C, 59.02; H, 4.54. Found: C, 59.14; H, 4.32.

Treatment of *trans* γ -Hydroxy enones (77a-d) with triethylamine. *trans* γ -Hydroxy enones (77a-d) in the presence of TEA (10 equiv.) gave quantitative formation of 1,4-dicarbonyls (59a-d). **A general procedure.** To a solution of *trans* γ -hydroxy enone (0.41 mmol) in dichloromethane (3 mL) was allowed to react with triethylamine (4.10 mmol) for 1 hour at ambient temperature. Subsequent removal of the volatiles *in vacuo* afforded the desired 1,4-dicarbonyl.

Compounds Described in Chapter 3

General procedure for preparation of *cis* γ -hydroxy enones (75a-e) and *cis* / *trans* cyclic hemiacetals (76a-e) from 1,2-dioxines (56a-e). The synthesis of *cis* γ -hydroxy enones (75a-e) and their corresponding *cis* / *trans* cyclic hemiacetals (76a-e) were produced via two methods from their parent 1,2-dioxines (56a-e). Limited spectral data was obtained for *cis* γ -hydroxy enones due to instability. Characterisation of *cis* / *trans* cyclic hemiacetals was not permitted due to significant signal overlap within ^1H NMR spectra and instability.

Method A. To a solution of the 1,2-dioxine (0.21 mmol) in dichloromethane (2 mL) at ambient temperature under nitrogen was added two drops of a solution of triethylamine in dichloromethane (0.069 M). Stirring was continued until cessation of reaction (as determined by TLC, approx. 2.5 hours) after which time the volatiles were removed *in vacuo*. The residue was immediately subjected to column chromatography using an 8 x 1.5 cm column. The volatiles were then removed *in vacuo* to afford a mixture of the *cis* γ -hydroxy enone (**75a-e**) and *cis* / *trans* cyclic hemiacetals (**76a-e**).

(Z)-4-Hydroxy-1,4-diphenyl-2-buten-1-one (75a). R_f 0.60 (2 : 1 hexane / ethyl acetate); ^1H NMR (CDCl_3 , 600 MHz) δ 2.68 (d, $J = 3.9$ Hz, exch. D_2O , 1H), 5.92 (ddd, $J = 7.5$, 3.9, 0.9 Hz, 1H), 6.55 (dd, $J = 11.7$, 7.5 Hz, 1H), 6.96 (dd, $J = 11.7$, 0.9 Hz, 1H), 7.25-7.7.59 (m, 8H), 7.97-8.00 (m, 2H).

(Z)-4-Hydroxy-1-phenyl-2-buten-1-one (75b). R_f 0.50 (3 : 2 hexane / ethyl acetate); IR (CDCl_3) 3446, 1662, 1608, 1521, 1448 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 3.15 (bs, exch. D_2O , 1H), 4.60 (dd, $J = 5.1$, 1.5 Hz, 1H), 6.63 (dt, $J = 12.0$, 5.1 Hz, 1H), 7.02 (dt, $J = 12.0$, 1.5 Hz, 1H), 7.25-7.7.59 (m, 8H), 7.97-8.00 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 61.1, 123.7, 128.5, 128.7, 133.2, 137.7, 147.8, 191.9.

(Z)-4-Hydroxy-1-phenyl-2-penten-1-one (75c). R_f 0.50 (3 : 2 hexane / ethyl acetate); ^1H NMR (CDCl_3 , 600 MHz) δ 1.40 (d, $J = 6.6$ Hz, 3H), 3.50 (d, $J = 3.6$ Hz, exch. D_2O , 1H), 4.88 (dddq, $J = 6.6$, 6.6, 3.6, 1.2 Hz, 1H), 6.43 (dd, $J = 12.0$, 6.6 Hz, 1H), 6.92 (dd, $J = 12.0$, 1.2 Hz, 1H), 7.45-7.60 (m, 3H), 7.94-7.98 (m, 2H).

(Z)-4-Hydroxy-1-[4-(trifluoromethyl)phenyl]-2-penten-1-one (75d). R_f 0.50 (3 : 2 hexane / ethyl acetate); ^1H NMR (CDCl_3 , 600 MHz) δ 1.40 (d, $J = 6.5$ Hz, 3H), 3.30 (bs, Hz, exch. D_2O , 1H), 4.93 (ddq, $J = 6.5$, 6.5, 1.5 Hz, 1H), 6.48 (dd, $J = 11.7$, 6.5, Hz, 1H), 6.89 (dd, $J = 11.7$, 1.5 Hz, 1H), 7.60-7.75 (m, 2H), 8.07-8.09 (m, 2H).

(Z)-5-Hydroxy-3-hexen-2-one (75e). (75e) and (*cis*-/*trans*-**76e**) were identified by comparison with the chemical and physical properties reported for the known compounds.¹⁰⁴

Method B. To a solution of the 1,2-dioxine (0.21 mmol) in dichloromethane (2 mL) at ambient temperature was added Co(SALEN)₂ (5 mg) and the mixture stirred for five hours. Samples were typically utilised without further purification as Co(SALEN)₂ showed no effect on cyclopropanation. Analytical samples were prepared by removal of the volatiles *in vacuo* and the residue triturated with hexane (3 x 5 mL). The extracts were combined and the volatiles were removed *in vacuo* to afford a mixture of the *cis* γ -hydroxy enones and *cis* / *trans* cyclic hemiacetals. Synthesis of the *cis* γ -hydroxy enones (**75a,e**) and *cis* / *trans* cyclic hemiacetals (**76a,e**) was carried out under the standard conditions outlined above.

The mixtures of *cis* γ -hydroxy enones (**75a-e**) and *cis* / *trans* cyclic hemiacetals (**76a-e**) were found to be extremely sensitive to facile dehydration to their corresponding furans.

Formation of 1,4-dicarbonyls (59a-e) from *cis* γ -hydroxy enones (75a-e) and *cis* / *trans* cyclic hemiacetals (76a-e). *cis* γ -Hydroxy enones (**75a-e**) and their corresponding *cis* / *trans* cyclic hemiacetals (**76a-e**) in the presence of TEA (10 equiv.) gave quantitative formation of 1,4-dicarbonyls (**59a-e**). 1,4-Dicarbonyl **2,5-hexanedione (59e)** was identified by comparison with the chemical and physical properties reported for the known compound.(ref aldrich spectra) **A general procedure.** To a thermodynamic mixture of *cis* γ -hydroxy enone and *cis* / *trans* cyclic hemiacetals (0.21 mmol) in dichloromethane (3 mL) was added triethylamine (2.10 mmol) and allowed to react for 10 minutes at ambient temperature. Subsequent removal of the volatiles *in vacuo* afforded the desired 1,4-dicarbonyl.

Formation of *trans* γ -hydroxy enones (77a-e) from *cis* γ -hydroxy enones (75a-e) and *cis* / *trans* cyclic hemiacetals (76a-e). *cis* γ -Hydroxy enones (**75a-e**) and their corresponding *cis* / *trans* cyclic hemiacetals (**76a-e**) in the presence of TPP (0.6 equiv.) gave quantitative formation of *trans* γ -hydroxy enones (**77a-e**). **A general procedure.** To a thermodynamic mixture of *cis* γ -hydroxy enone and *cis* / *trans* cyclic hemiacetals (0.21 mmol) in dichloromethane (3 mL) was added TPP (0.13 mmol) and allowed to react for 10 minutes at ambient temperature. Subsequent removal of the volatiles *in vacuo* afforded the desired of *trans* γ -hydroxy enone. Synthesis of all *trans* γ -hydroxy enones (**77a-e**) was carried out under the standard conditions outlined above.

(E)-5-Hydroxy-3-hexen-2-one (77e). Yield 98 mg, 98%; R_f 0.50 (3 : 2 hexane / ethyl acetate); ^1H NMR (CDCl_3 , 600 MHz) δ 1.36 (d, J = 6.6 Hz, 3H), 2.29 (s, 3H), 2.40 (bs, exch. D_2O , 1H), 4.52 (ddq, J = 6.6, 4.8, 1.8 Hz, 1H), 6.27 (dd, J = 16.0, 1.8 Hz, 1H), 6.80 (dd, J = 16.0, 4.8 Hz, 1H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 22.8, 27.4, 67.3, 128.5, 149.4, 198.8.

General procedure for the reaction of stabilised ylides (55a,c-e) with *cis* γ -hydroxy enones (75a-e) and *cis* / *trans* cyclic hemiacetals (76a-e). A mixture of *cis* γ -hydroxy enone (75a) and *cis* / *trans* cyclic hemiacetals (76a) (86 mg, 0.36 mmol) was allowed to react with benzyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (55c) (163 mg, 0.39 mmol) in anhydrous dichloromethane (5 mL) under an atmosphere of nitrogen at ambient temperature for 5 hours. Subsequent removal of the volatiles *in vacuo* afforded the crude cyclopropane 57c along with 1,4-dicarbonyl 59a. All examples, collated within Table 7 were carried out under the standard conditions outlined above. For reaction times and yields refer to Table 7. Column chromatography and subsequent recrystallisation from heptane, where applicable, afforded the pure cyclopropanes.

***trans* ($\pm$) Benzyl 2-(2-acetyl-3-methylcyclopropyl)acetate (112).** Yield 350 mg, 81 %; R_f 0.30 (4 : 1 hexane / ethyl acetate); IR (neat) 1734, 1694, 1498, 1259, 1169 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.10 (d, J = 6.0 Hz, 3H), 1.51 (dd, J = 4.2, 4.2 Hz, 1H), 1.65 (ddq, J = 9.6, 6.0, 4.2 Hz, 1H), 1.82 (dddd, J = 9.6, 8.8, 8.4, 4.2 Hz, 1H), 2.16 (s, 3H), 2.41 (dd, J = 16.8, 8.4 Hz, 1H), 2.49 (dd, J = 16.8, 8.8 Hz, 1H), 5.14 (s, 2H), 7.31-7.38 (m, 5H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 12.2, 23.2, 25.6, 30.3, 32.6, 36.4, 66.4, 128.1, 128.2, 128.5, 135.8, 171.9, 207.0; MS m/z (%): 246 (M^+ , 2), 186 (5), 155 (9), 91 (100); Anal. Calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3$ (246.3): C, 73.15; H, 7.37. Found: C, 73.34; H, 7.20.

***cis* ($\pm$) Benzyl 2-(2-acetyl-3-methylcyclopropyl)acetate (113).** Yield 52 mg, 12 % R_f 0.46 (4 : 1 hexane / ethyl acetate); IR (neat) 1736, 1691, 1558, 1390, 1166, 740, 698 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.14 (d, J = 6.4 Hz, 3H), 1.63 (ddq, J = 8.5, 8.5, 6.4 Hz, 1H), 1.74 (dddd, J = 8.5, 8.5, 8.2, 6.4 Hz, 1H), 2.11 (dd, J = 8.5, 8.5 Hz, 1H), 2.22 (s, 3H), 2.77 (dd, J = 17.6, 8.2 Hz, 1H), 2.84 (dd, J = 17.6, 6.4 Hz, 1H), 5.09 and 5.12 (ABq, J = 9.9 Hz, 2H), 7.30-7.37 (m, 5H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 6.9, 21.5, 23.0, 27.3,

27.3, 33.3, 66.2, 128.1, 128.1, 128.9, 136.1, 173.1, 207.6; MS m/z (%): 246 (M^+ , 2), 221 (8), 155 (32), 105 (48), 91 (100), 83 (30); HRMS of (**113**), $C_{15}H_{18}O_3$: calcd, 246.1256; found, 246.1259.

Benzyl (*E*)-4-methyl-6-oxo-6-methylhex-2-enoate (72d). Cyclopropane (**72d**) was heated in the neat form at 60 °C for 24 h, ^1H NMR analysis revealed α,β -unsaturated ester (**72d**) determined to be greater than 95 % pure. IR (neat) 1736, 1716, 1691, 1653 cm^{-1} ; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.07 (d, J = 7.2 Hz, 3H), 2.13 (s, 3H), 2.44 (dd, J = 17.1, 7.5 Hz, 1H), 2.55 (dd, J = 17.1, 6.3 Hz, 1H), 2.95-2.88 (m, 1H), 5.17 (s, 2H), 5.85 (dd, J = 15.9, 1.5 Hz, 1H), 6.93 (dd, J = 15.9, 7.2 Hz, 1H), 7.38-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 18.9, 30.5, 31.7, 49.1, 66.2, 119.8, 128.2, 128.3, 128.5, 136.0, 153.0, 166.4, 206.5; MS m/z (%): 246 (M^+ , 1), 155 (4), 91 (100), 82 (27), 43 (59); HRMS of (**z**), $C_{15}H_{19}O_3$: calcd, 247.1334; found, 247.1312.

Attempted synthesis of cyclopropanes (112) and (113). Dimethyl-3,6-dihydro-1,2-doxine (**53e**) (100 mg, mmol) was allowed to react with benzyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (**54c**) (mg, mmol) in dichloromethane (5 mL) at ambient temperature for 1 week. ^1H NMR analysis showed (**56e**) and (**55c**) unchanged.

Compounds Described in Chapter 4

(*E*)-1-phenyl-2-(3-phenyl-2-oxiranyl)-1-ethanone (114). (*E*)-1,4-Diphenyl-3-buten-1-one (**117**) was prepared by the action of phenyl magnesium bromide on the THF protected ester (**116**) of styryl acetic acid (**115**) according to the general procedure outlined by Rapoport *et. al.*¹¹⁹ To a solution of (**115**) (5.0 g, 30.8 mmol) in dichloromethane (120 mL) at -20 °C under nitrogen was added 2,3-dihydrofuran (2.26 g, 32.3 mmol) followed by methane sulphonic acid (6 mg, 0.062 mmol) as a solution in dichloromethane (0.4 mL). The mixture was allowed to reach 0 °C over 4 hours and was then recooled to -20 °C. Phenyl magnesium bromide (25 mL, 30.8 mmol, 1.23 M in ether) was then added dropwise to the solution over 5 minutes. Stirring was continued for 30 minutes, after which the mixture was allowed to warm to ambient temperature over 18 hours. The solution was then cooled to 0 °C and added dropwise into an aqueous solution

of H₃PO₄ (40 mL, 1.0 M) at 0 °C. The mixture was then allowed to attain ambient temperature after which it was diluted with water (30 mL) and dichloromethane (150 mL). The organic layer was removed and the aqueous phase washed with dichloromethane (3 x 30 mL). The organics were combined, dried and evaporated *in vacuo* to afford crude (**117**) which was purified by flash chromatography (R_f 0.5, 9 : 1 hexane / ethyl acetate). Recrystallization from hexane yielded pure (**117**) (3.28 g, 47 %) Mp: 83-84 °C Lit.¹¹⁸ Mp: 93 °C. Conversion of (**117**) into the titled compound (**114**) was achieved by *m*-CPBA oxidation as outline by Padwa.¹¹⁸ Mp: 102-103 °C (1 : 4 ether / hexane) Lit.¹¹⁸ Mp: 112-113 °C. IR (CHCl₃) 3500, 1670, 1597, 1549, 1448 cm⁻¹; ¹H NMR (CHCl₃, 600 MHz) δ 3.31 (1H, dd, *J* = 16.8, 5.0 Hz), 3.45 (1H, dd, *J* = 16.8, 5.8), 3.51 (1H, ddd, *J* = 5.8, 5.0, 2.0 Hz), 3.75 (1H, d, *J* = 2.0 Hz), 7.26-7.38 (3H, m), 7.48-7.51 (2H, m), 7.59-7.61 (1H, m), 7.97-7.99 (2H, m); ¹³C NMR (CHCl₃, 75 MHz) δ 41.9, 58.2, 58.4, 125.7, 128.1, 128.2, 128.4, 128.7, 133.4, 136.6, 136.8, 196.9.

Rearrangement of β,γ-epoxy ketone (114**) at high temperatures.** A solution of (*E*)-1-phenyl-2-(3-phenyl-2-oxiranyl)-1-ethanone (**114**) (40 mg, 0.17 mmol) in chloroform-*d* (0.7 mL) was heated at 50 °C for 4 days. Analysis of the sample showed 2,5-diphenylfuran (**58a**),¹⁵³ determined to be greater than 95% purity by ¹H NMR spectroscopy (300 MHz).

General procedure for the reaction of stabilised ylides (55c-e**) with β,γ-epoxy ketone (**114**).** (*E*)-1-phenyl-2-(3-phenyl-2-oxiranyl)-1-ethanone (**114**) (40 mg, 0.17 mmol) was allowed to react with benzyl 2-(triphenyl-λ⁵-phosphanylidene) acetate (**55c**) (69 mg, 0.17 mmol) in anhydrous chloroform-*d* (0.7 mL) at 50 °C for 14 days. Analysis of the sample was performed by ¹H NMR spectroscopy (300 MHz). All examples shown in Table 8 were carried out under the standard conditions outlined above. For reaction times and yields refer to Table 8.

Treatment of β,γ-epoxy ketone (114**) with triethylamine.** A solution of (*E*)-1-phenyl-2-(3-phenyl-2-oxiranyl)-1-ethanone (**114**) (40 mg, 0.17 mmol) and triethylamine (two drops of a solution of a 0.069 M dichloromethane) in chloroform-*d* (0.7 mL) was heated at 50 °C for 3 days. Removal of the volatiles *in vacuo* afforded 1,4-dicarbonyl (**59a**) (39 mg, 97 %).¹¹⁸

Treatment of β,γ -epoxy ketone (114) with *p*-TSA. A solution of (*E*)-1-phenyl-2-(3-phenyl-2-oxiranyl)-1-ethanone (**114**) (40 mg, 0.17 mmol) and *p*-TSA monohydrate (2 mg, 0.01 mmol) in chloroform-*d* (0.7 mL) was allowed to react for 5 minutes. The solution was subjected to column chromatography (1 x 0.25 cm). The volatiles were removed *in vacuo* to afford furan (**58a**) (35.5 mg, 96 %).¹⁵³

Synthesis of cyclopropane (57c) in the presence of deuterium oxide. A solution of 1,2-dioxine (**56a**) (130 mg, 0.55 mmol) in anhydrous dichloromethane (5 mL) was allowed to react with Co(SALEN)₂ (2 mg) for 1 hour under an atmosphere of nitrogen at ambient temperature. Benzyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (**55c**) (225 mg, 0.55 mmol) and deuterium oxide (0.5 mL) was then added and the mixture stirred vigorously for 5 days. The mixture was then dried over MgSO₄. Removal of the volatiles *in vacuo* and subsequent column chromatography (4 : 1 hexane / ethyl acetate) and recrystallisation (heptane) afforded the title compound (**57c**) (203 mg, 82 %). *trans* ($\pm$) **Benzyl 2-(2-benzoyl-3-phenylcyclopropyl)-2,2-dideuterioacetate (57c)**. *R*_f 0.50 (4 : 1 hexane / ethyl acetate); Mp 89-90 °C (heptane); IR 1727, 1663, 1598, 1164 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.35 (dd, *J* = 9.3, 4.9 Hz, 1H), 3.10 (dd, *J* = 4.9, 4.9 Hz, 1H), 3.13 (dd, *J* = 9.3, 4.9 Hz, 1H), 5.04 and 5.07 (AB_q, *J* = 12.6 Hz, 2H), 7.21-7.32 (m, 10H), 7.48-7.51 (m, 2H), 7.58-7.62 (m, 1H), 8.04-8.07 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 27.1, 29.3, 33.5, 66.4, 127.1, 128.2, 128.2, 128.3, 128.6, 128.7, 129.0, 133.1, 135.7, 135.9, 137.8, (one aromatic carbon masked), 172.0, 198.7; MS *m/z* (%): 372 (M⁺, 0.1), 280 (29), 105 (100), 105 (83), 91 (80)

Synthesis of cyclopropanes (66c) and (69c) in the presence of deuterium oxide. A solution of 1,2-dioxine (**536b**) (300 mg, 1.70 mmol) in anhydrous dichloromethane (10 mL), was allowed to react with benzyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (**55c**) (1.10 g, 2.70 mmol) and deuterium oxide (1 mL). The mixture was then stirred vigorously for 3 weeks after which time was then dried over MgSO₄. Removal of the volatiles *in vacuo* and subsequent column chromatography (4 : 1 hexane / ethyl acetate) and recrystallisation (heptane) afforded the cyclopropanes (**66c**) (390 mg, 74 %) and (**69c**) (58 mg, 11 %).

***trans* (±) Benzyl 2-(2-benzoyl-3-methylcyclopropyl)-2,2-dideuterioacetate (66c).** R_f 0.37 (4 : 1 hexane / ethyl acetate); Mp 53-55 °C (heptane); IR 1725, 1659, 1598, 1579 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.21 (d, $J = 6.6$ Hz, 3H), 1.87 (ddq, $J = 10.8, 6.6, 4.4$ Hz, 1H), 2.08 (dd, $J = 10.8, 4.4$ Hz, 1H), 2.26 (dd, $J = 4.4, 4.4$ Hz, 1H), 5.12 (s, 2H), 7.29-7.30 (m, 5H), 7.43-7.46 (m, 2H), 7.53-7.56 (m, 1H), 7.93-7.95 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 12.4, 24.4, 26.3, 32.5, 66.4, 127.9, 128.1, 128.2, 128.4, 128.5, 132.6, 135.7, 138.0, 171.9, 199.0; MS m/z (%): 310 (M^+ , 14), 219 (45), 105 (84), 91 (100)

***cis* (±) Benzyl 2-(2-benzoyl-3-methylcyclopropyl)-2,2-dideuterioacetate (69c).** R_f 0.42 (4 : 1 hexane / ethyl acetate); Mp 59-61 °C (heptane); IR 1727, 1657, 1594, 1577 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.21 (d, $J = 6.0$ Hz, 3H), 1.83 (ddq, $J = 8.8, 8.8, 6.0$ Hz, 1H), 1.93 (dd, $J = 8.8, 8.8$ Hz, 1H), 2.80 (dd, $J = 8.8, 8.8$ Hz, 1H), 5.08 and 5.10 (AB_q , $J = 12.6$ Hz, 2H), 7.28-7.33 (m, 5H), 7.42-7.46 (m, 2H), 7.53-7.56 (m, 1H), 7.90-7.94 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 7.3, 22.0, 23.1, 24.3, 66.1, 127.7, 128.0, 128.4, 128.5, 128.7, 132.3, 136.1, 139.8, 173.1, 199.5. HRMS of (69c), $\text{C}_{20}\text{H}_{18}\text{O}_3\text{D}_2$: calcd, 310.1539; found, 310.1544.

Treatment of cyclopropane (57c) with deuterium oxide. Cyclopropane (57c) was refluxed in THF / D_2O (5 mL, as a 2 : 1 mixture) for 24 hours. The solution was dried over MgSO_4 and the solvent removed *in vacuo*. ^1H NMR analysis revealed (57c) to be unchanged.

Compounds Described in Chapter 5

The *cis* / *trans* nomenclature utilised in naming cyclopropanes, arising from the secondary cyclopropane manifold, and their deuterio-analogues, refers to in the *cis* / *trans* orientation of H^3 (or CH_3 in the case of cyclopropane (73)) in relation to H^1 and H^2 of the cyclopropyl ring system, Scheme 68.

***cis* (±) Ethyl 1-methyl-2-(2-oxo-2-phenylethyl)-3-phenyl-1-cyclopropanecarboxylate (73).** A solution of 3,6-diphenyl-3,6-dihydro-1,2-dioxine (56a) (2.75 g, 11.6 mmol) in anhydrous dichloromethane (100 mL) was allowed to react with

(carboethoxyethylidene)triphenylphosphorane (**55d**) (4.2 g, 11.6 mmol) at ambient temperature, under an atmosphere of nitrogen for 6 days. Removal of the volatiles *in vacuo* afforded the crude cyclopropanes (**57d**) and (**73**) along with 1,4-dicarbonyl (**59a**). The crude material was subjected to column chromatography (5 : 1 hexane / ethyl acetate) and then again utilising (19 : 1 benzene / ether) as the eluant to yield (**73**) (260 mg, 7%). R_f 0.50 (19 : 1 benzene / ether); IR 1714, 1694, 1598, 1581 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.09 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.98 (ddd, $J = 7.2, 7.2, 6.6$ Hz, 1H), 2.87 (d, $J = 7.2$ Hz, 1H), 3.46 (dd, $J = 18.3, 6.6$ Hz, 1H), 3.53 (dd, $J = 18.3, 7.2$ Hz, 1H), 4.10-4.18 (m, 2H), 7.21-7.25 (m, 1H), 7.29-7.31 (m, 4H), 7.43-7.47 (m, 2H), 7.53-7.56 (m, 1H), 7.97-7.99 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 14.2, 16.0, 28.4, 29.5, 36.7, 37.0, 60.7, 126.7, 128.0, 128.2, 128.6, 129.4, 133.0, 136.9, 137.0, 174.1, 199.4; MS m/z (%): 323 (M^+ , 41), 277 (50), 203 (10), 105 (100); HRMS of (**73**) ($\text{C}_{22}\text{H}_{30}\text{O}_3$) calcd, 323.1647; found, 323.1659.

General procedure for the reaction of stabilised ylide (55h**) with 1,2-dioxines (**56a,c**).**

A mixture 1,2-dioxine (**56a**) (400 mg, 1.68 mmol) was allowed to react with *tert*-butyl 2-(triphenyl- λ^5 -phosphanyliden) acetate (**55c**) (698 mg, 1.70 mmol) in anhydrous dichloromethane (14 mL) under an atmosphere of nitrogen at ambient temperature for 3 days. Subsequent removal of the volatiles *in vacuo* and column chromatography afforded cyclopropanes (min) (51 mg, 9%), (norm) (85 mg, 15%), (maj) (373 mg, 66%), along with 1,4-dicarbonyl (**59a**). Analytical samples of cyclopropanes were prepared by recrystallisation from heptane. All examples were carried out under the standard conditions outlined above.

***trans* ($\pm$) *tert*-Butyl 2-(2-benzoyl-3-phenylcyclopropyl)acetate (**120**).** R_f 0.60 (4 : 1 hexane / ethyl acetate); Mp 100-101 $^\circ\text{C}$ (heptane); IR 1733, 1656, 1596, 1577 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.34 (s, 9H), 2.08 (dd, $J = 18.1, 10.3$ Hz, 1H), 2.26-2.31 (m, 2H), 3.06 (dd, $J = 4.9, 4.9$ Hz, 1H), 3.13 (dd, $J = 8.7, 4.9$ Hz, 1H), 7.25-7.27 (m, 3H), 7.31-7.33 (m, 2H), 7.49-7.52 (m, 2H), 7.58-7.60 (m, 1H), 8.07-8.08 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 27.8, 27.9, 29.6, 33.5, 34.5, 80.6, 126.9, 128.1, 128.4, 128.6, 128.9, 132.9, 136.1, 137.8, 171.2, 198.5; MS m/z (%): 336 (M^+ , 0.1), 281 (54), 221 (48), 105 (100), 77 (14), 57 (16); Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_3$ (336.4): C, 78.54; H, 7.19. Found: C, 78.78; H, 6.90.

***trans* (±) *tert*-Butyl-2-(2-oxo-2-phenylethyl)-3-phenylcyclopropane-1-carboxylate (118).** R_f 0.50 (4 : 1 hexane / ethyl acetate); Mp 69-71 °C (heptane); IR 1712, 1693, 1596, 1581 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.14 (s, 9H), 1.90 (dd, J = 9.6, 4.8 Hz, 1H), 2.42 (dd, J = 9.6, 5.4 Hz, 1H), 2.45 (dddd, J = 8.4, 5.4, 4.8, 4.8, 1H), 2.87 (dd, J = 16.8, 8.4 Hz, 1H), 3.43 (dd, J = 16.8, 4.8 Hz, 1H), 7.17-7.20 (m, 1H), 7.24-7.27 (m, 2H), 7.36-7.37 (m, 2H), 7.46-7.50 (m, 2H), 7.56-7.59 (m, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 19.9, 27.7, 28.8, 32.3, 41.8, 80.3, 126.6, 127.9, 128.1, 128.7, 129.6, 133.2, 136.6, 136.7, 169.6, 198.5; MS m/z (%): 336 (M^+ , 1), 281 (98), 263 (32), 105 (100), 77 (34); Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_3$ (336.4): C, 78.54; H, 7.19. Found: C, 78.48; H, 6.96.

***cis* (±) *tert*-Butyl-2-(2-oxo-2-phenylethyl)-3-phenylcyclopropane-1-carboxylate (119).** R_f 0.75 (4 : 1 hexane / ethyl acetate); Mp 70-72 °C (heptane); IR 1712, 1689, 1598, 1581 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.40 (s, 9H), 2.06 (dddd, J = 9.6, 7.7, 6.6, 6.0 Hz, 1H), 2.17 (dd, J = 9.6, 5.4 Hz, 1H), 2.45 (dd, J = 6.6, 5.4 Hz, 1H), 3.48 (dd, J = 18.2, 7.7 Hz, 1H), 3.52 (dd, J = 18.2, 6.0 Hz, 1H), 7.15-7.18 (m, 2H), 7.18-7.21 (m, 1H), 7.27-7.30 (m, 2H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 25.0, 28.1, 29.1, 30.9, 36.3, 80.8, 126.5, 128.0, 128.5, 128.6, 133.1, 137.0, 140.1, (one aromatic carbon masked), 171.3, 199.2; MS m/z (%): 336 (M^+ , 6), 280 (15), 105 (100), 77(39), 57 (51); Anal. Calcd for $\text{C}_{22}\text{H}_{24}\text{O}_3$ (336.4): C, 78.54; H, 7.19. Found: C, 78.31; H, 7.01.

Attempted isomerisation of cyclopropanes (118) and (119). A solution of cyclopropane (118) (20 mg) in anhydrous CDCl_3 (1 mL) was allowed to react with TPPO (10 mg) and *tert*-butyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (20 mg) for 2 days. ^1H NMR analysis revealed (118) to be unchanged. The identical reaction was performed using cyclopropane (119), with the same result.

***trans* (±) *tert*-Butyl 2-(2-benzoylcyclopropyl)acetate (123).** Yield 456 mg, 19%; R_f 0.60 (4 : 1 hexane / ethyl acetate); Mp 28-30 °C (heptane); IR (neat) 1730, 1668, 1599, 1579 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 0.98 (ddd, J = 8.1, 6.4, 4.1 Hz, 1H), 1.40 (s, 9H), 1.55 (ddd, J = 8.8, 4.8, 4.1 Hz, 1H), 1.85 (dddd, J = 8.8, 7.8, 6.4, 6.4, 4.8 Hz, 1H), 2.24

(dd, $J = 15.4, 7.8$ Hz, 1H), 2.46 (dd, $J = 15.4, 6.4$ Hz, 1H), 2.58 (ddd, $J = 8.1, 4.8, 4.8$ Hz, 1H), 7.45-7.48 (m, 2H), 7.54-7.57 (m, 1H), 7.99-8.01 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 17.5, 22.0, 24.3, 28.0, 39.5, 80.7, 128.0, 128.4, 132.7, 137.9, 171.0, 199.3; MS m/z (%): 260 (M^+ , 0.1), 205 (100), 187 (26), 105 (83), 77 (11), 57 (53); Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$ (260.3): C, 73.82; H, 7.74. Found: C, 73.50; H, 7.13.

***trans* ($\pm$) *tert*-Butyl-2-(2-oxo-2-phenylethyl)cyclopropane-1-carboxylate (121).** Yield 1.75 g, 73%; R_f 0.50 (4 : 1 hexane / ethyl acetate); Mp 71-72 °C (heptane); IR 1720, 1683, 1595, 1578 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 0.75 (ddd, $J = 8.3, 6.3, 4.5$ Hz, 1H), 1.24 (ddd, $J = 9.0, 4.5, 4.5$ Hz, 1H), 1.38-1.46 (m, 10H), 1.76 (dddd, $J = 9.0, 7.5, 6.3, 6.1, 4.1$ Hz, 1H), 2.82 (dd, $J = 16.8, 7.5$ Hz, 1H), 3.12 (dd, $J = 16.8, 6.1$ Hz, 1H), 7.45-7.47 (m, 2H), 7.55-7.58 (m, 1H), 7.92-7.93 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 14.9, 17.4, 21.4, 28.3, 42.3, 80.5, 128.3, 128.9, 133.3, 136.9, 173.1, 198.6; MS m/z (%): 260 (M^+ , 9), 204 (10), 187 (29), 105 (100), 77 (21), 57 (8); Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$ (260.3): C, 73.82; H, 7.74. Found: C, 73.97; H, 7.58.

***cis* ($\pm$) *tert*-Butyl-2-(2-oxo-2-phenylethyl)cyclopropane-1-carboxylate (122).** Yield 24 mg, 1%; R_f 0.65 (4 : 1 hexane / ethyl acetate); Mp 51-53 °C (heptane); IR 1714, 1687, 1594, 1577 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 0.93 (ddd, $J = 7.2, 5.4, 4.8$ Hz, 1H), 1.12 (ddd, $J = 8.7, 8.1, 4.8$ Hz, 1H), 1.38 (s, 9H), 1.67 (dddd, $J = 8.7, 8.7, 7.5, 7.2, 6.4$ Hz, 1H), 1.82, (ddd, $J = 8.7, 8.1, 5.4$ Hz, 1H), 3.29 (dd, $J = 18.0, 7.5$ Hz, 1H), 3.34 (dd, $J = 18.0, 6.4$ Hz, 1H), 7.43-7.46 (m, 2H), 7.53-7.56 (m, 1H), 7.93-7.95 (m, 1H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 13.0, 15.9, 18.8, 28.1, 36.6, 80.4, 128.0, 128.5, 132.9, 137.0, 172.4, 199.5; MS m/z (%): 260 (M^+ , 2), 205 (40), 187 (100), 105 (35), 77 (12), 57 (15); Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$ (260.3): C, 73.82; H, 7.74. Found: C, 74.12; H, 7.83.

Generation of a solution of intermediates A (124) and B (125). To a solution of 3,6-diphenyl-3,6-dihydro-1,2-dioxine (**56a**) (20 mg, 0.08 mmol) in anhydrous dichloromethane (1 mL), was added $\text{Co}(\text{SALEN})_2$ (1 mg) and *tert*-butyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (**55h**) (33 mg, 0.08 mmol). The mixture was stored at -15 °C for 2 days to yield a solution of intermediates **A** and **B** in a ratio of 7 : 3 respectively. Samples were typically utilised without further purification as $\text{Co}(\text{SALEN})_2$ showed no effect on cyclopropanation.

***tert*-Butyl 2-(5-hydroxy-2,5-diphenyltetrahydro-3-furanyl)-2-(1,1,1-triphenyl- λ^5 -phosphanylidene)acetate : Intermediate B (125).** To a mixture of 3,6-diphenyl-3,6-dihydro-1,2-dioxine (**56a**) (300 mg, 1.26 mmol) and *tert*-butyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (**55h**) (474 mg, 1.26 mmol) in acetonitrile (10 mL), was added bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (5 mg). The mixture was then allowed to react at $-15\text{ }^{\circ}\text{C}$ for 2 days after which time was allowed to attain ambient temperature. After 15 hours the solvent was decanted and crystalline (**125**) triturated with a small portion of cold acetonitrile to afford (**125**) (124 mg, 16 %). Mp $156\text{--}158\text{ }^{\circ}\text{C}$ (acetonitrile); IR 1593, 1378, 1014, 748, 694 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 0.98 (s, 9H), 2.03 (dddd, $J = 13.0, 8.4, 4.2\text{ Hz}$, $J_{\text{H-P}} = 13\text{ Hz}$, 1H), 2.40 (dd, $J = 13.0, 13.0\text{ Hz}$, 1H), 2.63 (dd, $J = 13.0, 4.2\text{ Hz}$, 1H), 5.34 (d, $J = 8.4\text{ Hz}$, 1H), 7.07-7.59 (m, 23H), 7.75-7.77 (m, 2H), 9.56 (s, exch. D_2O , 1H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 28.3, 40.4 (d, $J_{\text{C-P}} = 122.0\text{ Hz}$), 46.6 (d, $J_{\text{C-P}} = 12.6\text{ Hz}$), 49.4 (d, $J_{\text{C-P}} = 5.4\text{ Hz}$), 78.0, 82.4 (d, $J_{\text{C-P}} = 5.4\text{ Hz}$), 104.6, 125.3-133.4 (30 carbons), 142.5, 144.3, 169.9 (d, $J_{\text{C-P}} = 12.6\text{ Hz}$); ^{31}P NMR (CDCl_3 , 121.4 MHz) δ 24.29; MS m/z (%): 615 (M^+ , 0.1), 517 (60), 451 (28), 383 (81), 277 (78), 105 (100); Anal. Calcd for $\text{C}_{40}\text{H}_{39}\text{O}_4\text{P}$ (614.7): C, 78.16; H, 6.39. Found: C, 77.91; H, 6.54.

***tert*-Butyl 3-[hydroxy(phenyl)methyl]-5-oxo-5-phenyl-2-(1,1,1-triphenyl- λ^5 -phosphanylidene)pentanoate : Intermediate A (124).** Intermediate A (**124**) was characterised from analysis of a 7 : 3 sample of intermediates A and B respectively. Therefore, intermediate B (**125**) (20 mg) was dissolved in CDCl_3 (1.0 mL) and the sample allowed to reach equilibrium at $-15\text{ }^{\circ}\text{C}$ for 8 days, after which time the mixture was analysed. Ratio A : B (7 : 3). Data for A: IR (CHCl_3) 1672, 1596, 1438, 1104, 909 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 0.84 (s, 9H), 2.19 (ddd, $J = 14.4, 3.0\text{ Hz}$, $J_{\text{H-P}} = 1.8\text{ Hz}$, 1H), 2.48 (dddd, $J = 12.0, 3.0, 1.8\text{ Hz}$, $J_{\text{H-P}} = 18.0\text{ Hz}$, 1H), 4.53 (dd, $J = 14.4, 12.0\text{ Hz}$, 1H), 4.93 (brs, unresolved $^3J_{\text{H-H}}$ of 1.8 Hz and $^4J_{\text{H-P}}$ of 2.0 Hz, 1H), 6.66 (d, $J = 7.2\text{ Hz}$, 2H), 7.07-7.59 (m, 22H incl. OH), 7.83-7.84 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 28.2, 32.5 (d, $J_{\text{C-P}} = 7.5\text{ Hz}$), 43.1 (d, $J_{\text{C-P}} = 12.0\text{ Hz}$), 43.9 (d, $J_{\text{C-P}} = 116\text{ Hz}$), 77.8, 82.8 (d, $J_{\text{C-P}} = 3.3\text{ Hz}$), 125.3-138.0 (29 carbons), 144.4, 172.5, 203.3; ^{31}P NMR (CDCl_3 , 121.4 MHz) δ 23.99.

Rearrangement of *tert*-butyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (55h**) in the presence of deuterium oxide.** A solution of *tert*-butyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (**55h**) (200 mg) in anhydrous dichloromethane, was refluxed in the presence of deuterium oxide (1 mL) for 2 days. After which time analysis of the crude mixture by ^{31}P , ^{13}C , ^1H NMR spectroscopy revealed quantitative rearrangement to give TPPO and *tert*-butyl acetate- d_3 (**150**). *tert*-Butyl acetate- d_3 was identified by comparison with the known protio analogue.¹⁵¹

Synthesis of cyclopropanes (118**) and (**119**) in the presence of deuterium oxide.** A solution of 3,6-diphenyl-3,6-dihydro-1,2-dioxine (**56a**) (600 mg, 2.52 mmol) in anhydrous dichloromethane (10 mL), was allowed to react with *tert*-butyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (**55h**) (1.03 g, 2.52 mmol) and deuterium oxide (2 mL). The mixture was then stirred vigorously for 2 weeks after which time a further addition of *tert*-butyl 2-(triphenyl- λ^5 -phosphanylidene) acetate (**55h**) (1.03 g, 2.52 mmol) and deuterium oxide (1 mL) was required. The mixture was then stirred for a further 2 weeks, after which time was then dried over MgSO_4 . Removal of the volatiles *in vacuo* and subsequent column chromatography (4 : 1 hexane / ethyl acetate) afforded the cyclopropanes (**120**) (605 mg, 71%), (**118**) (119 mg, 14%) and (**119**) (34 mg, 4%). Analytical samples were obtained through recrystallisation from heptane.

***trans* ($\pm$) *tert*-Butyl 2-(2-benzoyl-3-phenylcyclopropyl)-2,2-dideuterioacetate (**120**).** R_f 0.60 (4 : 1 hexane / ethyl acetate); Mp 101-102 °C (heptane); ^1H NMR (CDCl_3 , 300 MHz) δ 1.34 (s, 9H), 2.28 (dd, $J = 4.5, 9.3$ Hz, 1H), 3.06 (dd, $J = 4.9, 4.9$ Hz, 1H), 3.13 (dd, $J = 8.7, 4.9$ Hz, 1H), 7.25-7.27 (m, 3H), 7.31-7.33 (m, 2H), 7.49-7.52 (m, 2H), 7.58-7.60 (m, 1H), 8.07-8.08 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 27.8, 27.9, 29.6, 33.5, 80.6, 126.9, 128.1, 128.4, 128.6, 128.9, 132.9, 136.1, 137.8, 171.2, 198.5; MS m/z (%): 338 (M^+ , 0.1), 221 (19), 105 (100), 77 (46), 57 (52).

***trans* ($\pm$) *tert*-Butyl-1-deuterio-2-(1-deuterio-2-oxo-2-phenylethyl)-3-phenyl cyclopropane-1-carboxylate (**118**).** R_f 0.50 (4 : 1 hexane / ethyl acetate); Mp 69-71 °C (heptane); IR 1712, 1693, 1598, 1582 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.14 (s, 9H), 2.42 (d, $J = 5.4$ Hz, 1H), 2.45 (dd, $J = 8.4, 5.4$ Hz, 1H), 3.42 (d, $J = 4.8$ Hz, 1H), 7.17-7.20 (m, 1H), 7.24-7.27 (m, 2H), 7.36-7.37 (m, 2H), 7.46-7.50 (m, 2H), 7.56-7.59 (m,

1H), 7.96-7.98 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 19.9, 27.7, 32.3, 41.3 (t, $J_{\text{D-C}} = 19.0$ Hz), 80.3, 126.6, 127.9, 128.1, 128.7, 129.6, 133.2, 136.6, 136.7, 169.6, 198.5; MS m/z (%): 338 (M^+ , 7), 282 (19), 105 (100), 77 (23), 57 (29).

***cis* (±) *tert*-Butyl-1-deuterio-2-(1-deuterio-2-oxo-2-phenylethyl)-3-phenylcyclopropane-1-carboxylate (119).** R_f 0.75 (4 : 1 hexane / ethyl acetate); Mp 70-72 °C (heptane); ^1H NMR (CDCl_3 , 300 MHz) δ 1.40 (s, 9H), 2.06 (dd, $J = 7.7, 6.6$ Hz, 1H), 2.45 (d, $J = 6.6$ Hz, 1H), 3.46 (d, $J = 7.7$ Hz, 1H), 7.15-7.18 (m, 2H), 7.18-7.21 (m, 1H), 7.27-7.30 (m, 2H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 25.0, 28.1, 30.9, 36.0 (t, $J_{\text{D-C}} = 19.4$ Hz), 80.8, 126.5, 128.0, 128.5, 128.6, 133.1, 137.0, 140.1, (one aromatic carbon masked), 171.3, 199.2; MS m/z (%): 336 (M^+ , 6), 280 (15), 105 (100), 77(39), 57 (51); HRMS of ($\text{C}_{22}\text{H}_{23}\text{O}_3\text{D}_2$ (+H)): calcd, 338.1850; found, 339.1928.

Synthesis of cyclopropanes (118) and (119) in the presence of deuterium oxide. 3,6-diphenyl-3,6-dihydro-1,2-dioxine (**56c**) (208 mg, 0.87 mmol) was converted into intermediates **A** and **B** utilising the previously described procedure. Deuterium oxide (2 mL) was then added and the mixture stirred vigorously for 5 days at ambient temperature under a nitrogen atmosphere. After which time the mixture was then dried over MgSO_4 , removal of the volatiles *in vacuo* and subsequent column chromatography (4 : 1 hexane / ethyl acetate) afforded the cyclopropanes (**118**) (230 mg, 78%) and (**119**) (50 mg, 17%). Analytical samples were obtained through recrystallisation from heptane.

***trans* (±) *tert*-Butyl-1-deuterio-2-(2-oxo-2-phenylethyl)-3-phenylcyclopropane-1-carboxylate (118).** R_f 0.50 (4 : 1 hexane / ethyl acetate); Mp 69-71 °C (heptane); ^1H NMR (CDCl_3 , 300 MHz) δ 1.14 (s, 9H), 2.42 (d, $J = 5.4$ Hz, 1H), 2.45 (ddd, $J = 8.4, 5.4, 4.8$ Hz, 1H), 2.87 (dd, $J = 16.8, 8.4$ Hz, 1H), 3.43 (dd, $J = 16.8, 4.8$ Hz, 1H), 7.17-7.20 (m, 1H), 7.24-7.27 (m, 2H), 7.36-7.37 (m, 2H), 7.46-7.50 (m, 2H), 7.56-7.59 (m, 1H), 7.96-7.98 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 19.9, 27.7, 32.3, 41.8, 80.3, 126.6, 127.9, 128.1, 128.7, 129.6, 133.2, 136.6, 136.7, 169.6, 198.5; MS m/z (%): 337 (M^+ , 1), 281, 264 (100), 105 (68), 77 (22), 57 (28).

***cis* (±) *tert*-Butyl-1-deuterio-2-(2-oxo-2-phenylethyl)-3-phenylcyclopropane-1-**

carboxylate (119). R_f 0.75 (4 : 1 hexane / ethyl acetate); Mp 70-72 °C (heptane); IR 1712, 1689, 1598, 1581 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.40 (s, 9H), 2.06 (ddd, J = 7.7, 6.6, 6.0 Hz, 1H), 2.45 (d, J = 6.6 Hz, 1H), 3.48 (dd, J = 18.2, 7.7 Hz, 1H), 3.52 (dd, J = 18.2, 6.0 Hz, 1H), 7.15-7.18 (m, 2H), 7.18-7.21 (m, 1H), 7.27-7.30 (m, 2H), 7.44-7.47 (m, 2H), 7.54-7.57 (m, 1H), 7.95-7.97 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 25.0, 28.1, 30.9, 36.3, 80.8, 126.5, 128.0, 128.5, 128.6, 133.1, 137.0, 140.1, (one aromatic carbon masked), 171.3, 199.2; MS m/z (%): 337 (M^+ , 0.1), 264 (17), 105 (100), 77 (44), 57 (45).

Treatment of cyclopropanes (118) and (119) with deuterium oxide. Cyclopropane (118) and (119) were individually refluxed in THF / D_2O (5 mL, as a 2 : 1 mixture) for 24 hours. The solution was dried over MgSO_4 and the solvent removed *in vacuo*. ^1H NMR analysis revealed (118) and (119) to be unchanged.

Rearrangement of intermediates A and B at high temperature. A solution of intermediates A and B was synthesised as previously discussed. Evaporation of the volatiles *in vacuo* was followed by the immediate addition of hot solvent (CHCl_3 or toluene). Refluxing for 20 minutes afforded cyclopropanes (118) and (119). For cyclopropyl ratio refer to Table 11.

Treatment of a solution of intermediates A and B with silica gel. 3,6-diphenyl-3,6-dihydro-1,2-dioxine (56a) (208 mg, 0.87 mmol) was converted into intermediates A and B utilising the above procedure. Silica gel (0.5 g) was then added, and the mixture stirred for 2 hours. Subsequent removal of the volatiles *in vacuo* and column chromatography allowed the isolation of γ -hydroxy ketone (138) (53 mg, 17%) and lactone (139) (188 mg, 77%).

***tert*-butyl 3-[hydroxy(phenyl)methyl]-5-oxo-5-phenylpentanoate (138).** R_f 0.30 (4 : 1 hexane / ethyl acetate); IR (neat) 3480, 1724, 1681, 1598, 1581 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 1.39 (s, 9H), 2.38 (dd, J = 16.2, 4.4 Hz, 1H), 2.40 (dd, J = 16.2, 2.8 Hz, 1H), 2.91 (dddd, J = 6.6, 6.6, 5.4, 4.4, 2.8 Hz, 1H), 3.05 (dd, J = 17.0, 6.6 Hz, 1H), 3.21 (dd, J = 17.0, 6.6 Hz, 1H), 3.23 (d, J = 5.4 Hz, exch. D_2O , 1H), 4.88 (dd, J = 5.4, 5.4 Hz, 1H), 7.24-7.27 (m, 1H), 7.30-7.37 (m, 4H), 7.42-7.45 (m, 2H), 7.53-7.56 (m, 1H), 7.91-7.93 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 28.0, 35.0, 38.5, 39.3, 75.5, 80.9, 126.3, 127.5,

128.2, 128.4, 128.6, 133.2, 137.0, 142.8, 173.2, 199.8. The titled compound **138** was found to be relatively unstable undergoing cyclisation to lactone **139** or decomposition.

trans (±) 4-(2-Oxo-2-phenylethyl)-5-phenyltetrahydro-2-furanone (139). R_f 0.15 (4 : 1 hexane / ethyl acetate); Mp 102-103 °C (3 : 2 hexane / ethyl acetate); IR 1772, 1682, 1595, 1577 cm^{-1} ; ^1H NMR (CDCl_3 , 600 MHz) δ 2.35 (dd, $J = 16.8, 7.2$ Hz, 1H), 3.00-3.09 (m, 2H), 3.15 (dd, $J = 17.4, 8.4$ Hz, 1H), 3.32 (dd, $J = 17.4, 5.4$ Hz, 1H), 5.22 (d, $J = 6.6$ Hz, 1H), 7.34-7.48 (m, 7H), 7.56-7.59 (m, 1H), 7.90-7.92 (m, 2H); ^{13}C NMR (CDCl_3 , 150 MHz) δ 34.8, 40.0, 40.6, 85.5, 125.9, 127.9, 128.7, 128.8, 133.6, 136.3, 137.9, 176.0, 197.3; MS m/z (%): 280 (M^+ , 6), 160 (50), 120 (82), 105 (100), 77 (52), 57 (15); Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{O}_3$ (280.3): C, 77.12; H, 5.75. Found: C, 76.95; H, 5.77.

Treatment of intermediate B (125) with silica. To a mixture of intermediate **B (125)** (100 mg, 0.16 mmol) in dichloromethane (10 mL) at ambient temperature, was added silica (200 mg) and the mixture stirred for 30 minutes after which time the silica was removed by filtration and the volatiles removed *in vacuo*. Subjecting the residue to column chromatography allowed for the isolation of γ -hydroxy ketone (**138**) (14 mg, 24 %) and lactone (**139**) (32 mg, 70 %).

Compounds Described in Chapter 6

Cobalt(II) acetate. Cobalt(II) acetate tetrahydrate (300 mg) was heated to 100 °C under vacume (0.01 Torr) for 6 hours to yield cobalt(II) acetate.

Co(II)-salen complex (143).¹³⁶ 3-*tert*-butyl-2-hydroxybenzaldehyde (**145**) (168 mg, 0.94 mmol) and (1*R*,2*R*)-(+)-1,2-diphenylethylenediamine (**146**) (100 mg, 0.47 mmol) were allowed to react in ethanol (2 mL) at ambient temperature under a nitrogen atmosphere for 24 hours. Removal of the volatiles *in vacuo* afforded crude ligand (**148**). The crude ligand was then allowed to react with cobalt(II) acetate (1 mL, 0.5 M solution in ethanol) under reflux for 9 hours. Removal of the volatiles *in vacuo*, filtration, washing with cold ethanol (1 mL) and drying *in vacuo* afforded the pure title compound (**143**) (206 mg, 74%).

Co(II)-salen complex (144).¹³⁷ 3-*tert*-butyl-2-hydroxybenzaldehyde (**145**) (156 mg, 0.88 mmol) and (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (**147**) (50 mg, 0.44 mmol) were allowed to react in ethanol (2 mL) at ambient temperature under a nitrogen atmosphere for 24 hours. Removal of the volatiles *in vacuo* afforded crude ligand (**149**). The crude ligand was then allowed to react with cobalt(II) acetate (1 mL, 0.5 M solution in ethanol) under reflux for 9 hours. Removal of the volatiles *in vacuo*, filtration, washing with cold ethanol (1 mL) and drying *in vacuo* afforded the pure title compound (**144**) (197 mg, 91%).

General procedure for the formation of cyclopropanes in the presence of chiral cobalt catalysts. A solution of 1,2-dioxine (**56a,f**) (100 mg) in dichloromethane was allowed to react with chiral cobalt catalyst (2 mol%). On obtaining complete conversion of the 1,2-dioxine into *cis* γ -hydroxy enone (**75a,f**) (determined by TLC analysis) the *cis* γ -hydroxy enone was allowed to react with ylide (1.1equiv.) for 5 days. Subsequent removal of the volatiles *in vacuo* and column chromatography afforded the requisite cyclopropanes. All examples are colated in Table 12.

CLS reagent analysis of cyclopropane (57c). europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate (20 mg) was added to a solution of cyclopropane (**57c**) (5 mg) in CCl₄ and benzene-*d*₆ (4 : 1). Ee determination was performed by ¹H NMR analysis of the benzyl CH₂ protons at δ 6.3 ppm.

CLS reagent analysis of cyclopropane (118). europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate (34 mg) was added to a solution of cyclopropane (**118**) (6 mg) in CCl₄ and benzene-*d*₆ (4 : 1). Ee determination was performed by ¹H NMR analysis of the *t*-butyl ester protons at δ 2.8 ppm.

CLS reagent analysis of cyclopropane (150). europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate (28 mg) was added to a solution of cyclopropane (**150**) (8.5 mg) in CCl₄ and benzene-*d*₆ (4 : 1). Ee determination was performed by ¹H NMR analysis of the benzyl CH₂ protons at δ 6.8 ppm.

Compounds Described in Chapter 7

***trans* (±) Phenyl-2-[2-(benzyloxy)-2-oxoethyl]-3-phenylcyclopropane-1-carboxylate (151).** To a mixture of (**57c**) (0.35 g, 0.94 mmol) in CH₂Cl₂ (4 mL) was added *m*-CPBA (0.58 g, 0.94 mmol, 70%) and the mixture stirred for two weeks after which time the insolubles were removed by filtration and a further portion of *m*-CPBA (0.58 g, 0.94 mmol, 70%) added. After a further two weeks the mixture was again filtered and the volatiles removed *in vacuo*. The residue was subjected to column chromatography to afford the di-ester (**151**) (0.33 g, 91%). *R*_f 0.50 (19 : 1 benzene / ether); IR (neat) 1745, 1732, 1594, 1494 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 2.26-2.29 (m, 4H), 3.05 (dd, *J* = 8.9, 5.7 Hz, 1H), 5.09 and 5.11 (AB_q, *J* = 12.4 Hz, 2H), 7.08-7.11 (m, 2H), 7.20-7.40 (m, 13H); ¹³C NMR (CDCl₃, 75 MHz) δ 24.5, 24.8, 31.3, 32.8, 66.4, 121.5, 125.8, 127.1, 128.1, 128.2, 128.5, 128.5, 128.9, 134.9, 135.7, (one aromatic carbon masked), 150.7, 171.5; MS *m/z* (%): 386 (M⁺, 1), 129 (6), 91 (100), 84 (11); Anal. Calcd for C₂₅H₂₂O₄ (386.5): C, 77.70; H, 5.74. Found: C, 77.54; H, 5.86.

***trans* (±) 2-(Carboxymethyl)-3-phenylcyclopropane-1-carboxylic acid (152).** To a solution of the di-ester (**151**) (104 mg, 0.27 mmol) was added a mixture of H₂O and methanol (5 mL, 1 : 4 v / v) followed by the introduction of an aqueous KOH solution (2.0 mL, 2M) and the solution stirred for 15 hours at ambient temperature. The mixture was then extracted with CH₂Cl₂ (2 x 5 mL) followed by acidification (conc. HCl) of the aqueous phase. Further extraction with CH₂Cl₂ (3 x 5 mL), desiccation and removal of the volatiles *in vacuo* afforded crude (**152**) which was further purified by recrystallization from dichloromethane / hexane (1 : 10) to afford pure di-acid (**152**) (59 mg, 99%). Mp 185-187 °C (dichloromethane / heptane); IR 1694, 1602, 1580 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.98 (dd, *J* = 16.8, 9.0 Hz, 1H), 2.07 (dd, *J* = 4.8, 4.8 Hz, 1H), 2.18 (dddd, *J* = 9.6, 9.0, 5.4, 4.8 Hz, 1H), 2.36 (dd, *J* = 16.8, 5.4 Hz, 1H), 2.96 (dd, *J* = 9.6, 4.8 Hz, 1H), 7.16-7.32 (m, 5H); ¹³C NMR (8 : 1; CDCl₃, / acetone-*d*₆, 75 MHz) δ 23.5, 23.9, 30.3, 31.8, 126.4, 127.9, 128.5, 135.1, 172.7, 174.0; MS *m/z* (%): 220 (M⁺, 19), 202 (22), 174 (23), 129 (100), 115 (60), 91 (34); HRMS of (**152**) C₁₂H₁₂O₄ (+H): calc, 221.0814; found: 221.0804.

Baeyer-Villiger oxidation of (118). To a mixture of (118) (0.20 g, 0.60 mmol) in CH₂Cl₂ (3 mL) was added *m*-CPBA (0.22 g, 0.9 mmol, 70%) and the mixture stirred for five days after which time the insolubles were removed by filtration and the volatiles removed *in vacuo*. The residue was subjected to column chromatography to afford the di-esters (153) (50 mg, 24%) and (154) (115 mg, 55%).

***trans* (±) [2-(*tert*-Butoxycarbonyl)-3-phenylcyclopropyl]methyl benzoate (153).** *R_f* 0.60 (4 : 1 hexane / ethyl acetate); Mp 92-93 °C (heptane); IR 1712, 1601, 1583 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.16 (s, 9H), 2.08 (dddd, *J* = 7.2, 6.8, 6.3, 5.3 Hz, 1H) 2.65 (dd, *J* = 9.8, 6.8 Hz, 1H), 4.32 (dd, *J* = 11.4, 7.2 Hz, 1H), 4.51 (dd, *J* = 11.4, 6.3 Hz, 1H), 7.20-7.28 (m, 5H), 7.43-7.49 (m, 2H), 7.55-7.60 (m, 1H), 8.06-8.09 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 22.9, 27.8, 27.9, 30.3, 66.0, 80.6, 126.8, 128.0, 128.4, 129.4, 129.8, 130.1, 133.0, 135.8, 166.5, 168.8; MS *m/z* (%): 352 (M⁺, 2), 296 (100), 279 (94), 175 (49), 144 (23); Anal. Calcd for C₂₂H₂₄O₄ (352.4): C, 74.97; H, 6.86. Found: C, 74.87; H, 6.99.

***trans* (±) *t*-Butyl-2-(2-oxo-2-phenoxyethyl)-3-phenylcyclopropane-1-carboxylate (154).** *R_f* 0.50 (4 : 1 hexane / ethyl acetate); Mp 126-127 °C (heptane); IR 1759, 1713, 1589 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 1.15 (s, 9H), 1.96 (dd, *J* = 9.6, 4.8 Hz, 1H), 2.43-2.58 (m, 3H), 2.98 (dd, *J* = 15.3, 4.8 Hz, 1H), 7.08 - 7.12 (m, 2H), 7.19- 7.29 (m, 4H), 7.33 - 7.41 (m, 4H); ¹³C NMR (CDCl₃, 75 MHz) δ 20.1, 27.8, 29.0, 32.0, 37.6, 80.5, 121.5, 125.9, 126.8, 128.0, 129.5, 129.5, 136.1, 150.7, 169.2, 170.5; MS *m/z* (%): 352 (M⁺, 0.1), 296 (78), 279 (100), 185 (38), 129 (49), 115 (76); Anal. Calcd for C₂₂H₂₄O₄ (352.4): C, 74.97; H, 6.86. Found: C, 74.66; H, 6.65.

***trans* (±) 2-[2-(*tert*-Butoxycarbonyl)-3-phenylcyclopropyl]acetic acid (155).** To a mixture of the di-ester (154) (97 mg, 0.28 mmol) was added a mixture of H₂O and methanol (5 mL, 1 : 4 v / v) followed by the introduction of an aqueous KOH solution (2.0 mL, 2M) and the solution stirred for 15 hours at ambient temperature. Water was then added (5 mL) and the mixture extracted with CH₂Cl₂ (2 x 5 mL) followed by acidification (conc. HCl) of the aqueous phase. Further extraction with CH₂Cl₂ (3 x 5 mL), desiccation and removal of the volatiles *in vacuo* afforded crude (155) which was further purified by recrystallisation to afford pure mono-acid (155) (61 mg, 79%). Mp

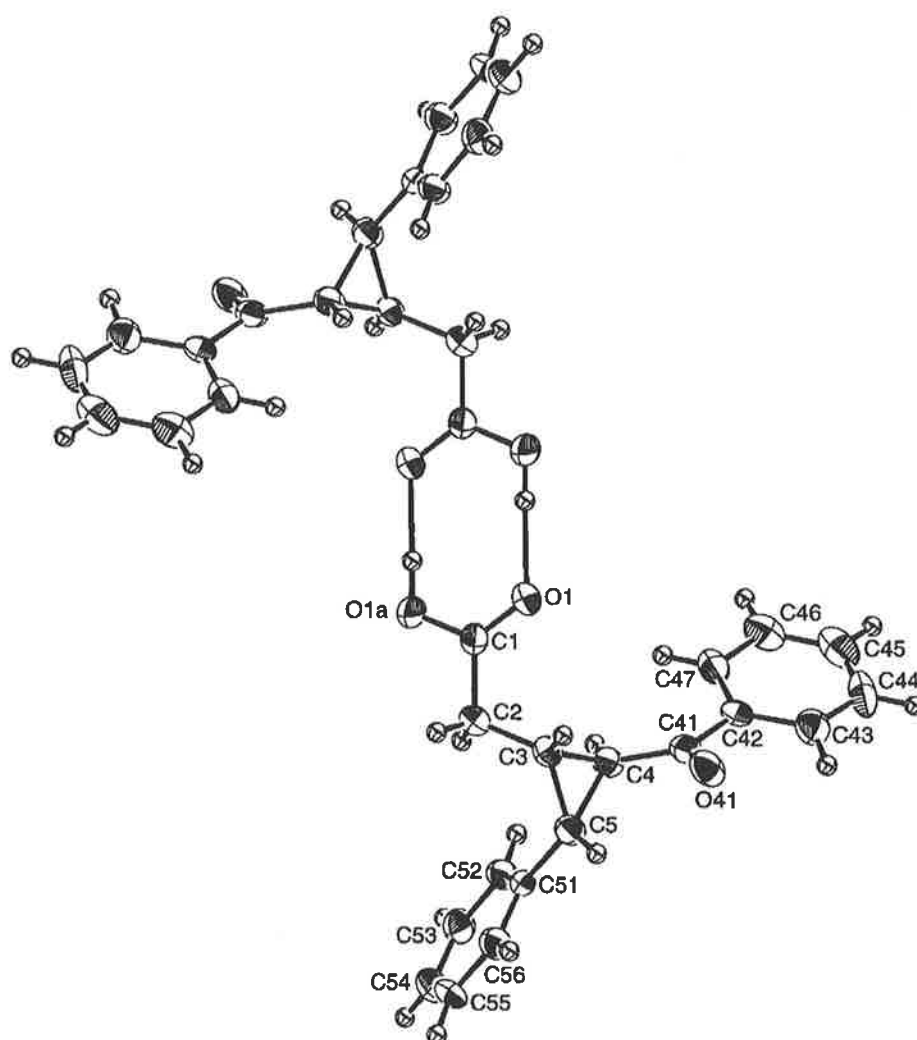
147-148 °C (1 : 8 dichloromethane / hexane); IR 1716, 1706, 1602 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 1.14 (s, 9H), 1.88 (dd, $J = 9.5, 4.5$ Hz, 1H), 2.27-2.37 (m, 2H), 2.46 (dd, $J = 9.5, 6.0$ Hz, 1H), 2.78 (dd, $J = 19.8, 8.7$ Hz, 1H), 7.19-7.33 (m, 5H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 19.6, 27.8, 29.0, 31.9, 37.1, 80.5, 126.7, 127.9, 129.4, 136.1, 169.3, 177.6; MS m/z (%): 276 (M^+ , 1), 221 (48), 203 (40), 129 (59), 57 (100); Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4$ (276.3): C, 69.54; H, 7.29. Found: C, 69.50; H, 7.33.

***trans* (±)2-(Carboxymethyl)-3-phenylcyclopropane-1-carboxylic acid (156).** To a mixture of the mono-ester (**155**) (50 mg, 0.18 mmol) in CDCl_3 (1 mL) was added trifluoroacetic acid (2 drops) and solution left standing for 15 hours at ambient temperature. Removal of the volatiles *in vacuo* followed by recrystallisation afforded pure di-acid (**156**) (38 mg, 95%). Mp 140-141 °C (1 : 10, dichloromethane / heptane); IR 1694, 1599, 1410 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 2.09 (dd, $J = 9.6, 5.3$ Hz, 1H), 2.47 (dddd, $J = 7.5, 6.6, 6.6, 5.3$ Hz, 1H), 2.60 (dd, $J = 17.1, 7.5$ Hz, 1H), 2.70 (dd, $J = 9.6, 6.6$ Hz, 1H), 2.75 (dd, $J = 17.1, 6.6$ Hz, 1H), 7.24-7.31 (m, 5H); ^{13}C NMR (8 : 1, CDCl_3 / acetone- d_6 , 75 MHz) δ 20.8, 27.2, 32.4, 36.6, 126.3, 127.6, 128.9, 135.6, 172.2, 173.6; MS m/z (%): 220 (M^+ , 30), 174 (28), 129 (100), 115 (60), 91 (27); Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{O}_4$ (220.2): C, 65.45; H, 5.49. Found: C, 65.53; H, 5.50.

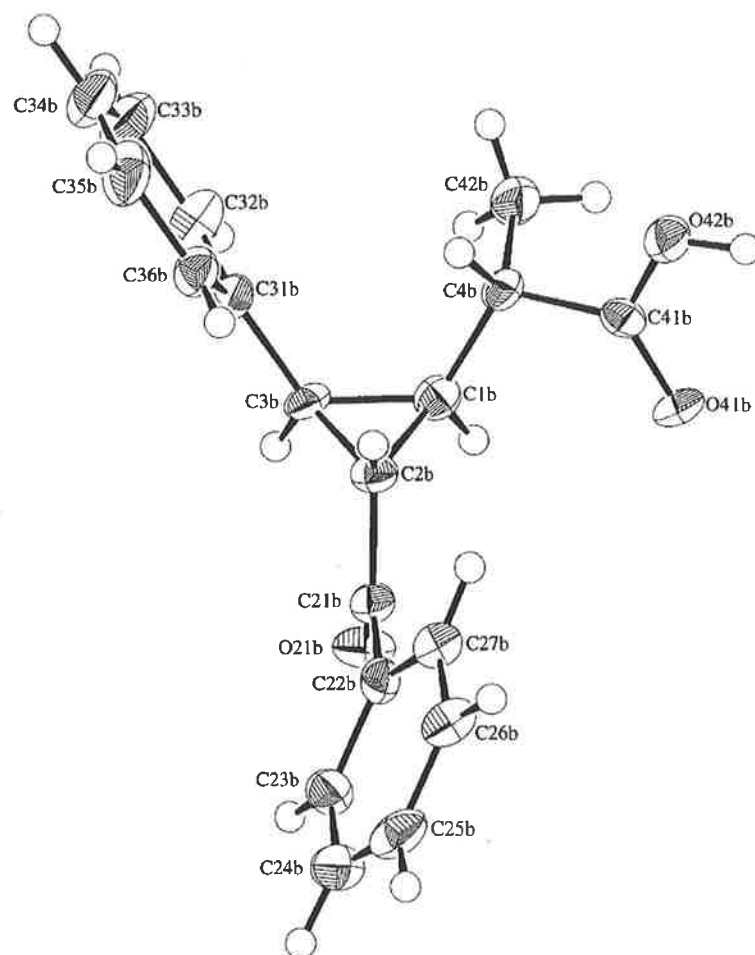
Baeyer-Villiger oxidation of (119). To a mixture of (**119**) (0.3 g, 0.90 mmol) in CH_2Cl_2 (5 mL) was added *m*-CPBA (0.55 g, 2.25 mmol, 70%) and the mixture stirred for eleven days after which time the insolubles were removed by filtration and the volatiles removed *in vacuo*. The residue was then subjected to column chromatography (ethylacetate / hexane, 1 : 4) to afford the inseparable di-esters (**157**) and (**158**) in a relative ratio of 1 : 2. To these di-esters was added a mixture of H_2O and methanol (5 mL, 1 : 4 v / v) followed by the introduction of an aqueous KOH solution (2.0 mL, 2M) and the solution stirred for 15 hours at ambient temperature. Water was then added (5 mL) and the mixture extracted with CH_2Cl_2 (2 x 5 mL) followed by acidification (conc. HCl) of the aqueous phase. Further extraction with CH_2Cl_2 (3 x 5 mL), desiccation and removal of the volatiles *in vacuo* afforded a crude mixture of the mono-acids (**159**) and (**160**) in a relative ratio of 1 : 2. These acids were then taken up in CH_2Cl_2 (3 mL) and treated with trifluoroacetic acid (1.5 mL) over four days at ambient temperature. A further portion of CH_2Cl_2 (2 mL) was then added and the organics washed with saturated bicarbonate (2 x 10 mL). Desiccation

of the organic phase and removal of the volatiles *in vacuo* afforded the known lactone (**162**) (22 mg, > 99 % purity). The combined aqueous washings were acidified to pH = 1 with concentrated HCl and then extracted with CH₂Cl₂ (3 x 10 mL) to afford the crude di-acid (**161**) contaminated with some benzoic acid. Removal of the benzoic acid was achieved by sublimation (80 °C / 0.01 mmHg) and the di-acid further purified by recrystallization from heptane to afford pure (**161**) (48 mg, 24%). Mp 127-129 °C (1 : 10, dichloromethane / heptane); IR 1712, 1687, 1602, 1580 cm⁻¹; ¹H NMR (acetone-*d*₆, 300 MHz) δ 2.14 (dddd, *J* = 9.0, 7.5, 6.9, 6.6 Hz, 1H), 2.27 (dd, *J* = 9.0, 5.0 Hz, 1H), 2.58 (dd, *J* = 6.6, 5.0 Hz, 1H), 2.93 (dd, *J* = 17.4, 7.5 Hz, 1H), 3.02 (dd, *J* = 17.4, 6.9 Hz, 1H), 7.32-7.49 (m, 5H); ¹³C NMR (acetone-*d*₆, 75 MHz) δ 25.3, 26.9, 30.9, 31.0, 126.1, 126.2, 128.1, 139.9, 171.8, 172.5; MS *m/z* (%): 221 (M⁺+H, 42), 203 (100), 185 (22); HRMS of (**30**) C₁₂H₁₂O₄ (+H): calc, 221.0814; found: 221.0814.

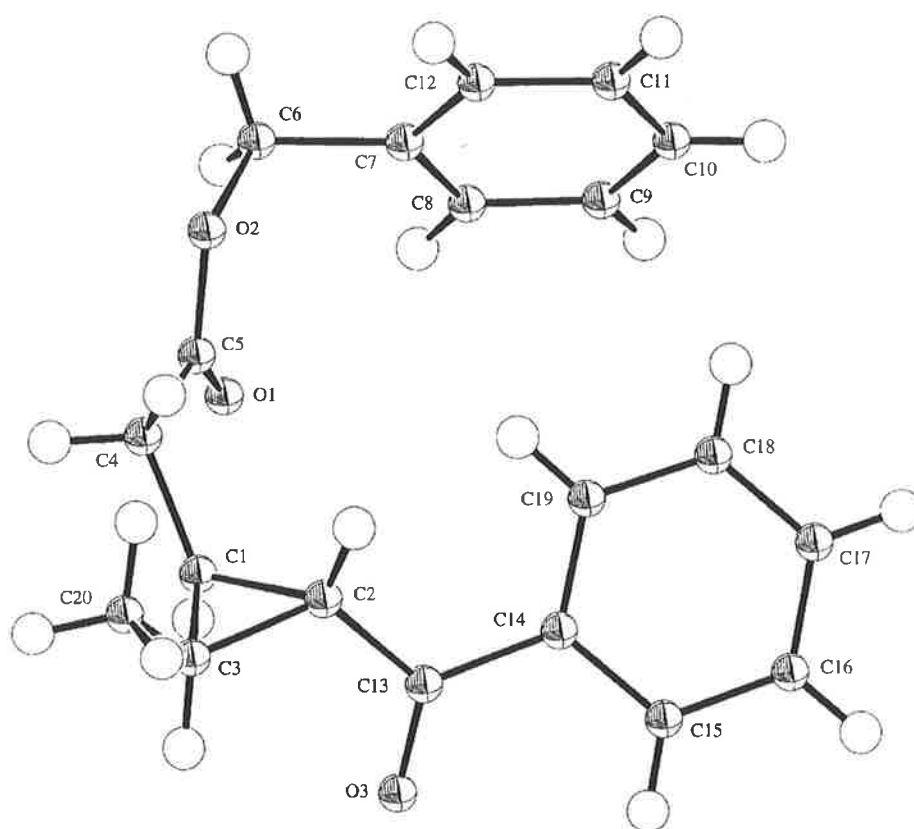
Appendix 1



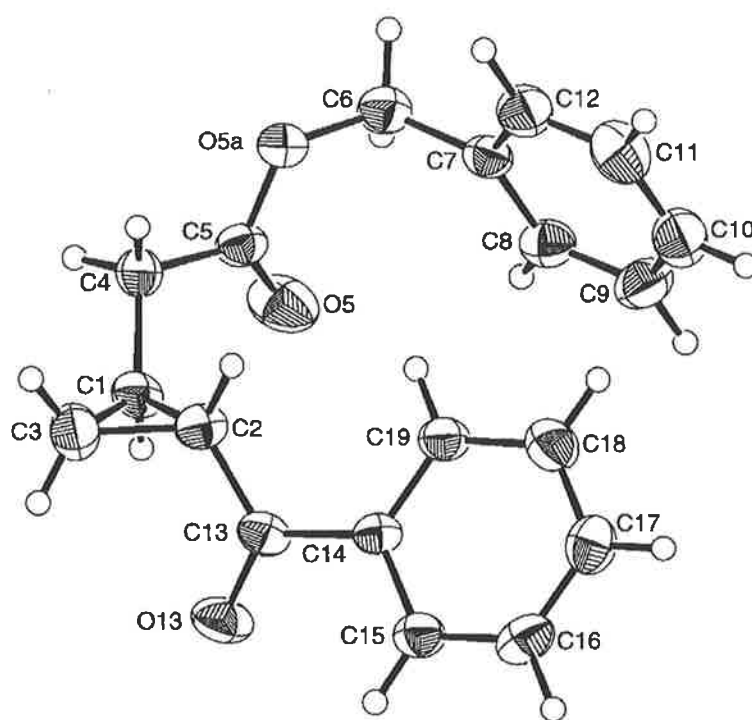
Molecular structure of cyclopropane (**64**).



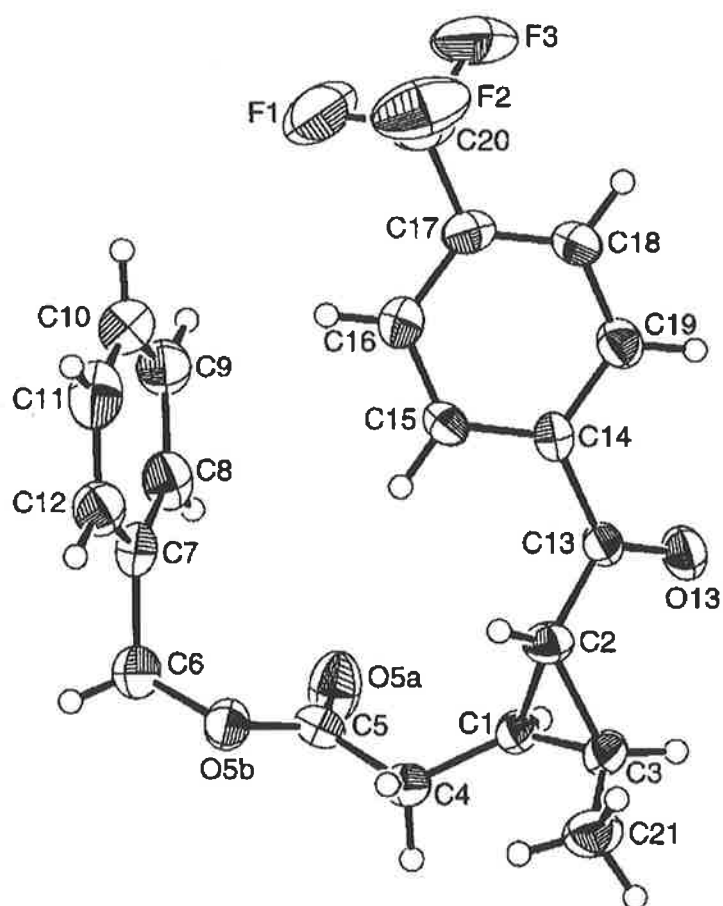
Molecular structure of cyclopropane (**74**).



Molecular structure of cyclopropane (**66c**).

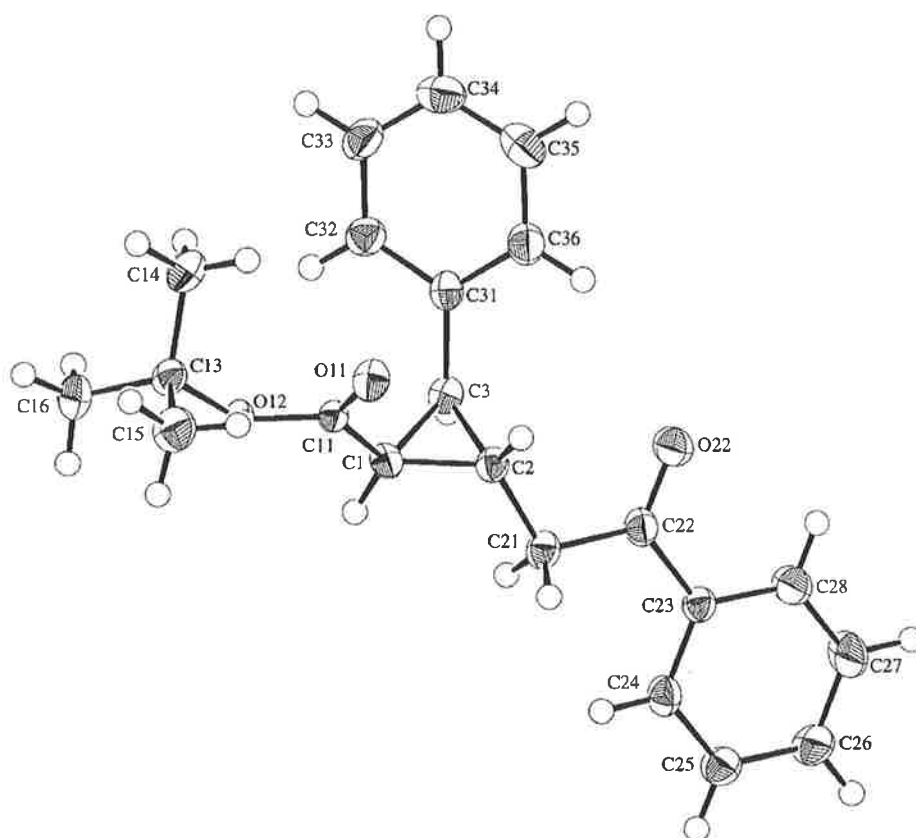


Molecular structure of cyclopropane (**67c**).

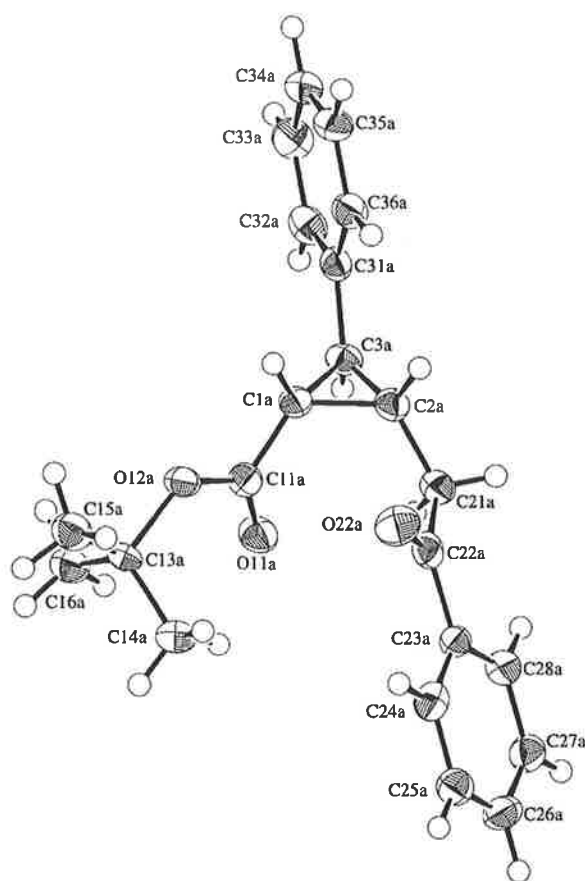


Molecular structure of cyclopropane (**68c**).

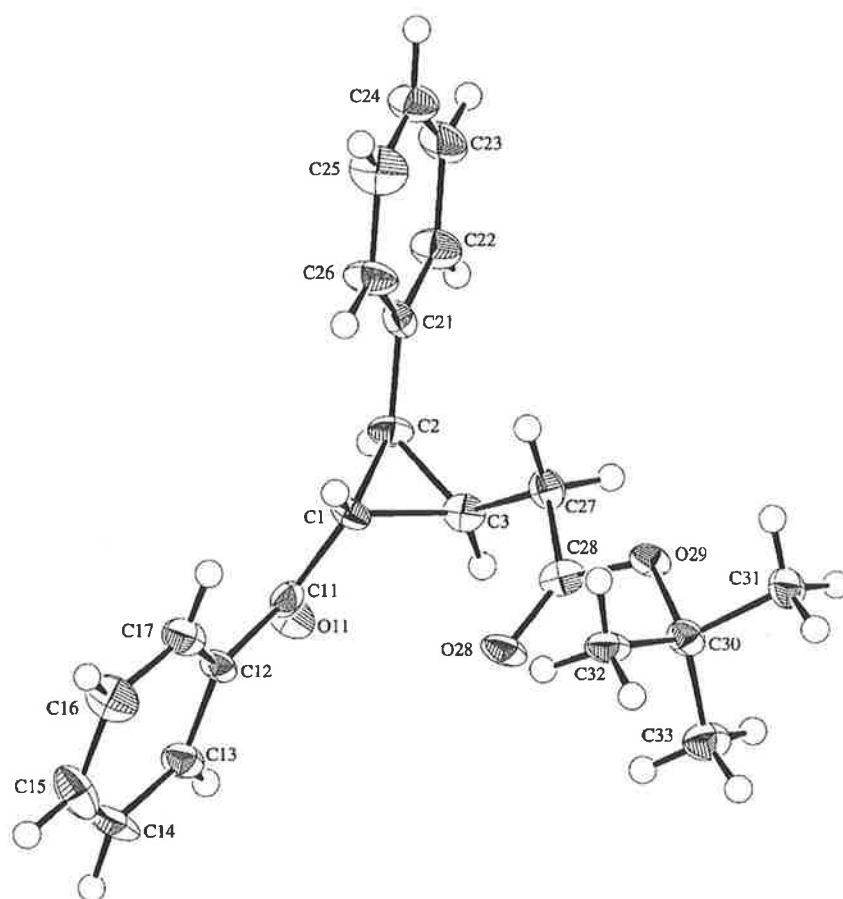
Appendix 2



Molecular structure of cyclopropane (**118**).

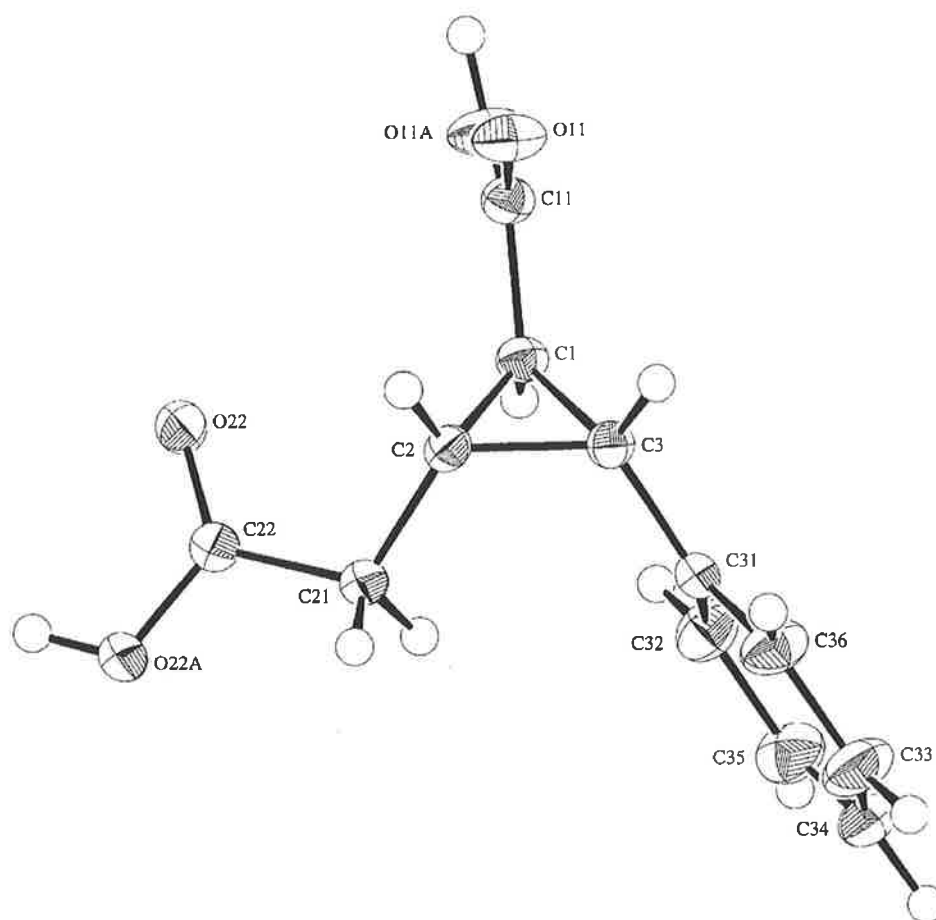


Molecular structure of cyclopropane (**119**).

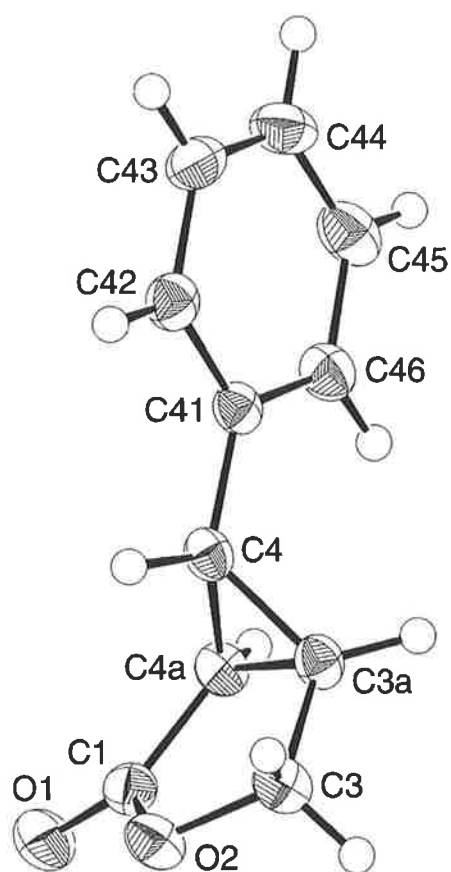


Molecular structure of cyclopropane (**120**).

Appendix 3



Molecular structure of cyclopropane (**152**).



Molecular structure of cyclopropane (**162**).

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Exploitation of ylide steric bulk to alter cyclopropanation outcome during the reaction of 1,2-dioxines and stabilised phosphorus ylides

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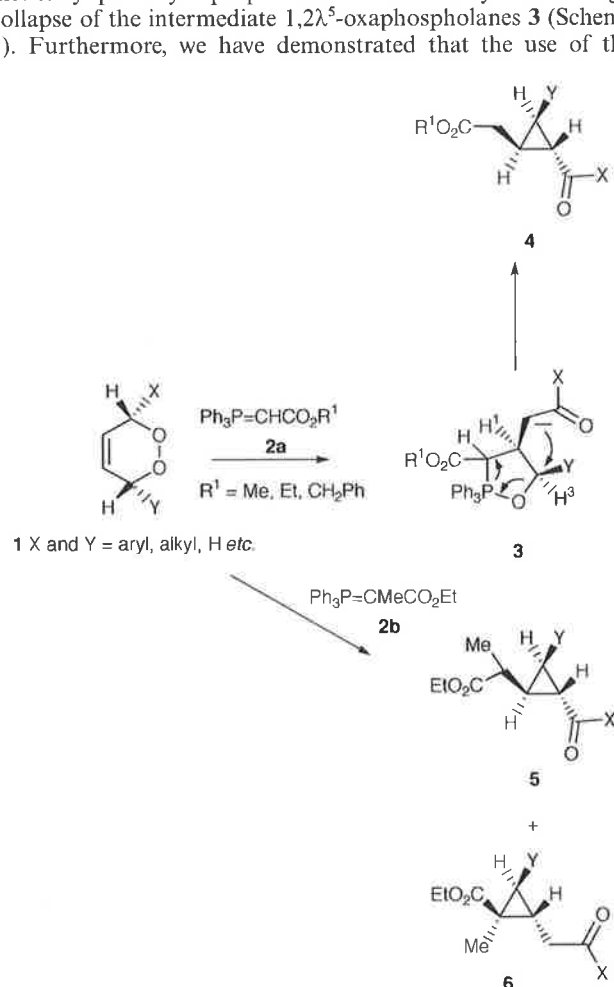
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A new approach for the synthesis of diastereomerically pure cyclopropanes from 1,2-dioxines and sterically bulky stabilised phosphorus ylides is presented.

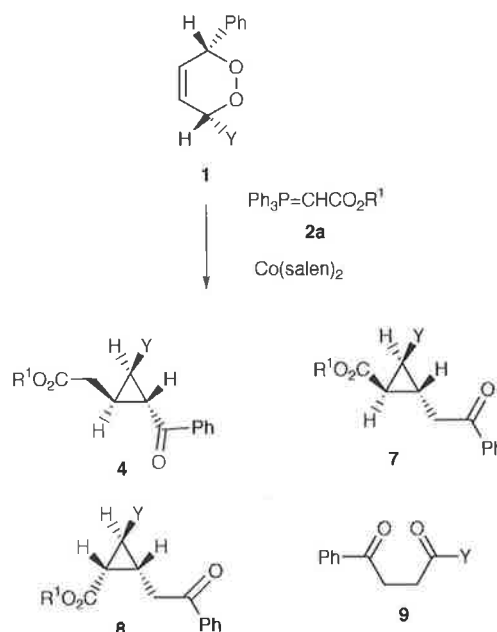
Organics containing the cyclopropane motif are of wide interest since many display novel biological activity, whilst others have been utilised as key intermediates in the synthesis of natural and non-natural products. Through a series of mechanistic studies we have elucidated a clear understanding of the complex relationship between 1,2-dioxines, and their isomeric *cis* and *trans* γ -hydroxy enones, *cis* and *trans* hemiacetals and β -ketoepoxides, and of how these precursors can be utilised to construct diastereomerically pure or enantiomerically pure diversely functionalised cyclopropanes.¹ We now 'expect' that the reaction of 1,2-dioxines **1** with stabilised phosphorus ylides containing an ester moiety **2a**, will afford diastereomerically pure cyclopropanes **4** in excellent yields through collapse of the intermediate 1,2 λ^5 -oxaphospholanes **3** (Scheme 1). Furthermore, we have demonstrated that the use of the

bulkier di-substituted ylide **2b** allows for the incorporation of another stereogenic centre within the side chain of the cyclopropane **5**. However, during these investigations we also isolated (7%) another cyclopropane **6** which did not appear to originate from our proposed mechanism and we speculated that the steric bulk of the ylide may be the reason behind the formation of **6**. We now report on the exploitation of the steric bulk of the ester moiety of the stabilised ylides to completely alter the diastereomeric course of these cyclopropanation reactions.

We began analysing the effect of steric bulk on cyclopropanation outcome with the diphenylmethyl (DPM) grouping. Thus, reaction of 1,2-dioxine **1** (Y = Ph) with ylide **2a** (R¹ = Ph₂CH) under the conditions specified within Table 1 (entry 1), resulted only in the formation of diastereomerically pure cyclopropane **4** (Scheme 2). Hence the DPM grouping fails to alter



Scheme 1



Scheme 2

the cyclopropanation outcome. A far more dramatic effect on cyclopropanation outcome was found during investigations utilising the *tert*-butyl ester stabilised ylide (entries 2–4, Table 1). Thus, reaction of 1,2-dioxine **1** (Y = Ph) with ylide **2a** (R¹ = *t*-Bu) at 25 °C resulted in the formation of three cyclopropyl isomers (entry 3). The first of these was simply the 'expected' *trans*-cyclopropane **4** resulting from collapse of the 1,2 λ^5 -oxaphospholane **3**, while the remaining two (**7** and **8**) represented a uniquely different cyclopropanation outcome. The structure and relative stereochemistry of these two new cyclopropanes were unambiguously elucidated from a combination of crystallography and ¹H, ¹³C, gCOSY, gHSQC, and

Table 1 Reaction of 1,2-dioxines **1** with various bulky ylides **2**^a

Entry	Y	R ¹	Solvent	Conc./M	Temp./°C	Cyclopropane (yield, %)	9 (yield, %)
1	Ph	Ph ₂ CH	CH ₂ Cl ₂	0.38	25	4 (97) 7 (0) 8 (0)	3
2 ^b	Ph	<i>t</i> -Bu	CDCl ₃	0.08	−15	4 (0) 7 (91) 8 (9)	0
3	Ph	<i>t</i> -Bu	CH ₂ Cl ₂	0.40	25	4 (19) 7 (70) 8 (8)	3
4	Ph	<i>t</i> -Bu	CDCl ₃	0.08	60	4 (33) 7 (52) 8 (6)	9
5 ^b	Ph	1-Ad	CDCl ₃	0.06	−15	4 (12) 7 (67) 8 (20)	0
6	Ph	1-Ad	CDCl ₃	0.06	25	4 (30) 7 (61) 8 (9)	0
7	Ph	1-Ad	CDCl ₃	0.15	25	4 (58) 7 (35) 8 (5)	2
8	Ph	1-Ad	CDCl ₃	0.06	60	4 (42) 7 (45) 8 (6)	7
9	Ph	1-Ad	Toluene	0.06	100	4 (75) 7 (5) 8 (0)	20
10 ^c	H	<i>t</i> -Bu	CH ₂ Cl ₂	0.12	−15	4 (48) 7 (49) 8 (2)	0
11	H	<i>t</i> -Bu	CH ₂ Cl ₂	0.54	25	4 (77) 7 (22) 8 (1)	0
12	H	<i>t</i> -Bu	CDCl ₃	0.12	60	4 (81) 7 (14) 8 (5)	0
13	H	1-Ad	CHCl ₃	0.1	25	4 (19) 7 (64) 8 (17)	0
14	H	1-Ad	CHCl ₃	0.06	60	4 (79) 7 (18) 8 (3)	0

^a 1-Ad refers to 1-adamantyl. Yields quoted refer to those determined from analysis of the crude mixtures by ¹H NMR (600 MHz). Isolated yields were within a few percent of the values given. General procedure for reactions performed at ambient and higher temperatures: the 1,2-dioxine **1** and ylide (1 equiv.) were combined in the appropriate solvent at the concentration specified and the mixture stirred under nitrogen for 3 days. The solvent was removed *in vacuo* and the residue subjected to flash chromatography (ethyl acetate–hexane, 1:4) to afford the observed products. ^b A catalytic amount (5 mol%) of Jacobson's catalyst was also added at −15 °C. The mixture was kept at this temperature for 2 days after which time it was allowed to warm to room temperature and was analysed. ^c Triethylamine (1 equiv.) added at −15 °C. The mixture was kept at this temperature for 3 days after which time it was allowed to warm to room temperature and was analysed.

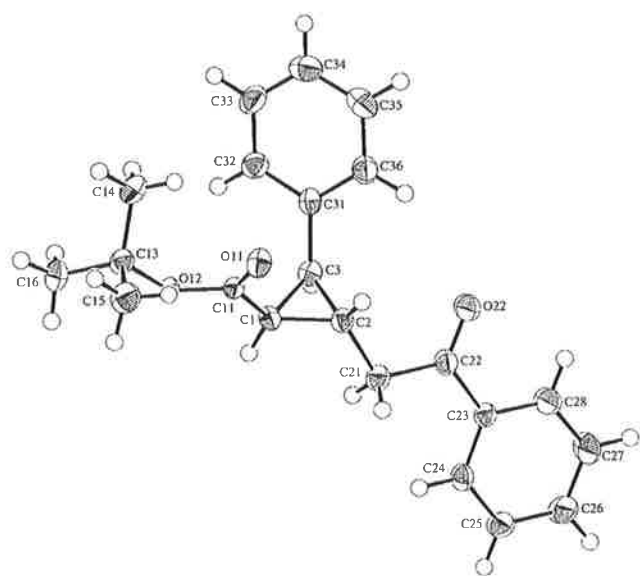


Fig. 1 Molecular structure of **7** (Y = Ph, R¹ = *t*-Bu) showing the crystallographic numbering scheme employed: O(11)–C(11)–C(1)–C(2) 1.1(4)°, O(22)–C(22)–C(21)–C(2) 1.1(3)° and C(32)–C(31)–C(3)–C(1) −69.2(3)°.

gHMBC NMR techniques.[†] Fig. 1 represents the molecular structure of **7** (Y = Ph, R¹ = *t*-Bu).^{‡,2}

To rule out the possibility that the minor cyclopropane **8** was formed first under the reaction conditions, and then isomerised to **7**, we treated isolated cyclopropane **8** with excess ylide under identical reaction conditions (with triphenylphosphine oxide present) and found no isomerisation. We next analysed the effect of temperature on reaction outcome. Performing the identical reaction at 60 °C resulted in an increase in yield of the 'normal' *trans*-cyclopropane **4** at the expense of cyclopropanes (**7** and **8**) (entry 4). A slight increase in the yield of 1,4-diketone **6** was also noticed and is expected at elevated temperatures through a competing Kornblum–De La Mare rearrangement.³ We have previously reported the use of Co(salen)₂ (salen = 2,2'-[ethane-1,2-diylbis(nitrilomethylidyne)]dibenzenethiolato) or Jacobson's catalyst to dramatically accelerate these cyclopropanation reactions.¹ These catalysts rapidly induce rearrangement of the 1,2-dioxines to their corresponding *cis* γ-hydroxy enones which are the key intermediates required for cyclopropanation.⁴ Hence we next performed the identical reaction at −15 °C in the presence of a catalytic amount (5 mol%) of Jacobson's catalyst (entry 2). At this temperature none of the

'normal' *trans*-cyclopropane isomer **4** was detected whilst the yield of **7** had increased to 91%.

In order to further evaluate the effect of ylide steric bulk on cyclopropanation outcome we investigated the use of the 1-adamantyl ester which has a slightly smaller cone angle than the *tert*-butyl moiety (entries 5–9). Utilisation of this ylide **2a** (R¹ = 1-Ad) resulted in a decrease in yield of (**7** and **8**) with a concomitant increase in the yield of the 'normal' *trans* isomer **4** (compare entries 6 and 3). Performing the reaction at elevated temperature once again favoured the formation of the 'normal' *trans*-cyclopropane **4** (entries 8 and 9) while lower temperatures were found to favour the formation of **7** and **8** (entry 5). An important observation was that simply increasing the overall reaction concentration favours the formation of the 'normal' *trans*-cyclopropane over **7** and **8** (compare entries 6 and 7). In addition, we have previously noticed that the sterics and electronics of the substituent Y within the 1,2-dioxines **1** have little effect on cyclopropanation outcome and as such we anticipated that this new route to diastereomerically pure cyclopropanes of type **7** would be applicable to a wide range of substituents.¹ This assumption was verified with the use of 1,2-dioxine **1** (Y = H) which afforded the di-substituted cyclopropanes **4** and **7** in good yields at elevated and sub-ambient temperatures respectively (entries 10–14). Once again, the use of sterically bulky ester ylides under concentrated conditions favours the formation of the 'normal' *trans* isomer **4** while dilute conditions favour the formation of **7** and **8**.

Finally, monitoring the reaction between 1,2-dioxine (**1**, Y = Ph) with the *tert*-butyl ester ylide (entry 3) by ³¹P NMR at 20 °C revealed the initial formation of two phosphorus containing intermediates corresponding to signals at 23.99 and 24.29 ppm.[§] These two intermediates which were in a relative ratio of *ca.* 9:1, respectively, then decayed over 12 hours to afford the observed cyclopropanes **7**, **8** and TPPO. These chemical shifts are inconsistent with a neutral pentavalent oxaphospholane ring of type **3** and are more appropriately assigned as being due to charged species.⁵ The exact nature of these intermediates is yet to be fully established.

We conclude that the steric bulk of the ester moiety of stabilised phosphorus ylides has a dramatic effect on cyclopropanation outcome observed during the reaction between 1,2-dioxines and stabilised ester ylides. Whereas previously, utilisation of sterically 'non-bulky' ylides (*e.g.* Me, Et, Bn) afforded the 'normal' *trans* diastereomerically pure cyclopropanes **4** in excellent yields at ambient temperature, we now find that sterically bulky ylides (*e.g.* *t*-Bu, 1-Ad) favour the formation of a different diastereomeric cyclopropyl series at these temperatures. The mechanism is currently being fully investigated and will be reported in due course.

Acknowledgements

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Notes and references

† All new compounds have been fully characterised by elemental analysis, spectroscopy and mass spectrometry.

‡ *Crystal data*: $C_{22}H_{24}O_3$, **7** ($Y = Ph$, $R^1 = t-Bu$): monoclinic $P2_1/n$, $a = 5.5486(1)$, $b = 17.8452(8)$, $c = 19.0424(8)$ Å, $\beta = 91.930(3)^\circ$, $U = 1884.4(1)$ Å³, $Z = 4$, $D_c = 1.186$ g cm⁻³ and $\mu = 0.77$ cm⁻¹. Data were collected at 173 K on a Nonius Kappa CCD employing Mo-K α radiation in the ranges $1.0^\circ < \theta < 30.1^\circ$ and $1.4^\circ < \theta < 27.5^\circ$, respectively. The structure was solved by SAPI91 and refined with the TEXSAN Structure Analysis Package (Molecular Structure Corporation, 1998) of crystallographic programs. A total of 2484 reflections with $I \geq 3.0\sigma(I)$ were used in the refinement which converged with $R = 0.073$ and $R_w = 0.047$. CCDC reference number 207/411. See <http://www.rsc.org/suppdata/p1/b0/b001975p/> for crystallographic files in .cif format.

§ ³¹P NMR chemical shifts referenced to 85% aqueous H₃PO₄ (external)

in CDCl₃. No such signals are observable for the reaction of the same 1,2-dioxine with non-bulky ylides, ref. 1.

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- 2 The crystal structure of cyclopropane **4** ($Y = Ph$, $R^1 = t-Bu$) has been submitted for publication elsewhere; T. D. Avery, G. Fallon, D. K. Taylor and E. R. T. Tiekink, *Z. Kristallogr.*, 2000, in the press. Cyclopropane **8** ($Y = Ph$, $R^1 = t-Bu$) has been submitted for publication elsewhere; T. D. Avery, G. Fallon, D. K. Taylor and E. R. T. Tiekink, submitted for publication in *Z. Kristallogr.*, 2000.
- 3 N. Kornblum and H. E. De La Mare, *J. Am. Chem. Soc.*, 1951, **73**, 881; M. E. Sengül, Z. Ceylan and M. Balci, *Tetrahedron*, 1997, **53**, 10401 and references cited therein. Also see ref. 1.
- 4 K. E. O'Shea and C. S. Foote, *J. Org. Chem.*, 1989, **54**, 3475. Also see ref. 1.
- 5 See for example: J. C. Hanekamp, R. B. Rookhuizen, H. J. T. Bos and L. Brandsma, *Tetrahedron*, 1992, **48**, 5151; W. Adam, H. M. Harrer and A. Treiber, *J. Am. Chem. Soc.*, 1994, **116**, 7581 and references cited therein.

New synthetic methodology utilising 1,2-dioxines and stabilised phosphorus ylides: a highly diastereoselective cyclopropanation reaction

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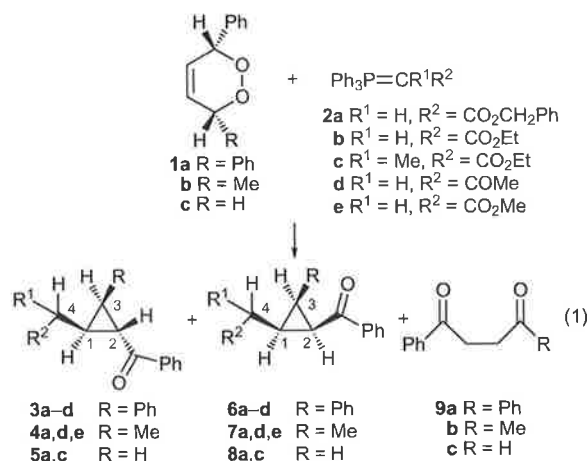
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A new method is described for the synthesis of diastereomerically pure cyclopropanes from substituted 1,2-dioxines **1a–c** and stabilised phosphorus ylides **2a–e**.

In 1994 the group of Adam and Treiber established for the first time that the peroxide bond of 1,2-dioxetanes is susceptible to nucleophilic 'attack' by simple diazoalkanes.¹ In this first report, 1,2-dioxetanes upon treatment with diazoalkanes afforded a mixture of products including 1,3-dioxolanes. More recently, the reactions between various methyl-substituted 1,2-dioxetanes and simple triphenylalkylidenephosphoranes were explored by the same group.² Initial nucleophilic 'attack' on the O–O linkage was proposed for the observed formation, at low temperature, of 2,2,2-triphenyl-1,4,2λ⁵-dioxaphosphorinanes which, upon warming, ring-opened affording dipolar phosphonium alkoxides.

Herein we report that various 1,2-dioxines **1a–c** react under mild conditions with stabilised phosphorus ylides **2a–e** to afford novel diastereomerically pure cyclopropanes [reaction (1)]. To



the best of our knowledge, the reactions of stabilised phosphorus ylides with 1,2-dioxines have not been reported until now. A typical reaction involved treatment of **1a**³ with **2a** (1.1 equiv.) in an appropriate solvent (usually CH₂Cl₂) at ambient temperature. The major product formed was identified as the cyclopropane **3a** along with a trace of diketone **9a**⁴. Similar reactions afforded a variety of di- and tri-substituted cyclopropanes in excellent yields and are collated in Table 1. Compounds **1a** and **c** afforded essentially diastereomerically pure *trans*-cyclopropanes whilst **1b** afforded the *trans*-cyclopropane as the major diastereomer along with a minor amount of the *cis*-cyclopropane. Typically the isolated yields were within 10% of those quoted whilst the diastereomers were easily separated by column chromatography. The structure and relative stereochemistry of the cyclopropanes were unambiguously elucidated from a combination of ¹H, ¹³C, DEPT, NOESY (¹H-COSY and HMQC with gradient coherence selection)

Table 1 Reaction of 1,2-dioxines **1a–c** with various stabilised phosphorus ylides **2a–e** at 25 °C^a

1,2-Dioxine	Ylide	Yield of cyclopropane (%)		Yield of 9 (%)
1a	2a	3a (95)	6a (≤2)	9a (3)
	2b	3b (96)	6b (≤2)	9a (2)
	2c	3c (48)	6c (nd)	9a (52)
	2d	3d (nd)	6d (nd)	9a (100)
1b	2a	4a (84)	7a (15)	9b (≤1)
	2d	4d (75)	7d (15)	9b (10)
	2e	4e (82)	7e (18)	9b (nd)
	2c	5a (100)	8a (nd)	9c (nd)
1c	2a	5a (100)	8a (nd)	9c (nd)
	2c	5c (80)	8c (nd)	9c (nd) ^b

^a All reactions performed in CH₂Cl₂; yields were determined from the ¹H NMR spectra (600 MHz) of the crude reaction mixtures; nd denotes not detectable. ^b Another unidentified minor product present.

NMR techniques.† X-Ray analysis† of **4a** (Fig. 1) unambiguously confirmed the general structural and stereochemical assignments elucidated by NMR spectroscopy.

The effect of solvent and additives on the rate of reaction between **1a** and **2a** and the cyclopropane : diketone ratio **3a** : **9a** was evaluated. Our initial findings indicate that the overall rate of reaction increases only slightly with increasing solvent polarity. The small rate increase is inconsistent with a mechanism involving zwitterionic intermediates in the rate-determining step. The relative rate and product ratio was unaffected by the addition of TEMPO suggesting that free radicals are not involved. Additionally, the formation of 'free' carbenes can be excluded on the basis that addition of excess cyclohexene failed to compete in cyclopropane formation. This

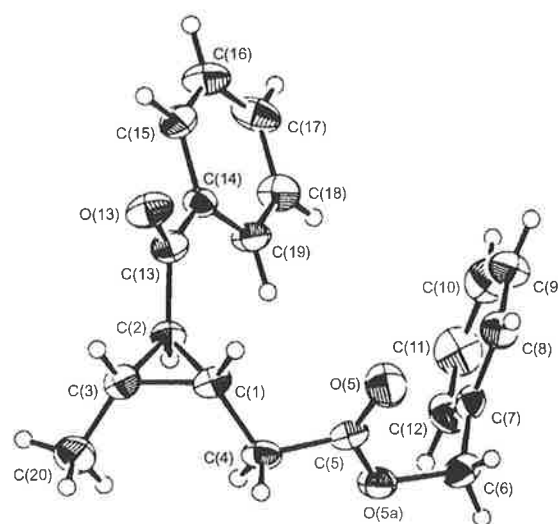


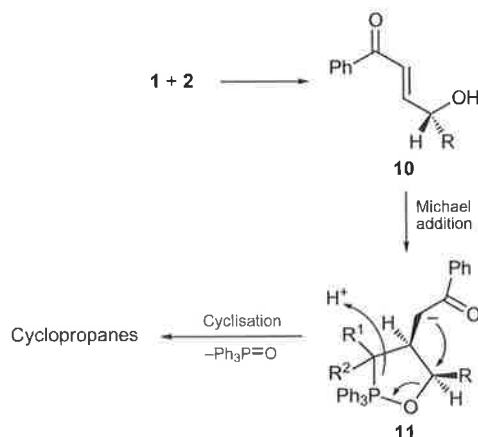
Fig. 1 Molecular structure of **4a** showing the crystallographic numbering scheme employed: O(5)–C(5)–C(4)–C(1) 34(1)°, C(5)–O(5a)–C(6)–C(7) –82.6(8)°, C(2)–C(13)–C(14)–C(15) 159.5(7)°

conclusion was further supported by the observation that only a trace of the carbene dimer (<1%) could be detected by ^1H NMR analysis of the crude reaction mixtures. Finally, performing the reaction at 80 °C simply lead to an increased rate without a change in product outcome or ratio.

The reaction of equimolar amounts of **1a** and **2a** in C_6D_6 was monitored by ^{31}P NMR spectroscopy. At no time could any 'free' triphenylphosphine or zwitterionic intermediates be detected. Careful ^1H NMR analysis of the crude mixture after cessation of the reaction revealed the presence of **3a**, **9a**, Ph_3PO and unreacted **2a**. All **1a** had been consumed affording **3a** and **9a** in a 77:22 ratio. The remaining 1% constituted the *cis*-cyclopropane. Formation of Ph_3PO (75%) parallels the yield of the cyclopropane as expected. Most important was the observation that 22% unreacted **2a** remained and parallels **9a** formation (22%). This observation suggests that formation of **9a** is catalytic in ylide. Indeed, analysis of all crude reaction mixtures by ^{31}P and ^1H NMR spectroscopies showed the same trend. Blank reactions showed that formation of **9a-c** was not promoted by Ph_3PO . We have evidence that the rearrangement **1a** $\rightarrow$ **9a** is not promoted by 'free' Ph_3P liberated during the ylide reaction, e.g. addition of excess Ph_3P to the reaction mixture containing **1a** and **2a** failed to dramatically change product outcome. Based on these initial findings we suggest that formation of **9a** in the reaction of **1a** with **2a** is promoted by the ylide acting as a weak base⁵ in a catalytic manner. Base catalysed rearrangement (Kornblum-De La Mare decomposition) of cyclic peroxides has been reported previously and is initiated by removal of a proton from the carbon adjacent to the O-O linkage.⁶ Finally, the observation that the more sterically hindered **2c** affords less cyclopropane **3c** when compared to that for **2b** in identical solvents suggests that there is a steric component to the two competing processes.

A significant mechanistic finding was the observation of the *trans*-alcohol **10** intermediate during ^1H NMR monitoring of these reactions. Indeed, we were able to isolate a quantity of **10** from the reaction mixture and demonstrate that it lead to the observed cyclopropanes and no 1,2-diketone upon addition of ylid. Although the reaction manifold is complicated by many factors, Scheme 1 depicts a general mechanistic overview. Interaction of **1** and **2** leads in a rate-limiting step to the formation of the key intermediate **10**. Michael addition of the ylide to **10**, followed by cyclisation, proton transfer and extrusion of triphenylphosphine oxide from **11** affords the observed cyclopropanes. In competition with this process is the known cyclisation⁶ of (*Z*)-**10** via the hemi-acetal and rearrangement leading to formation of **9**.

Synthetically, this novel reaction has several advantages over existing methods⁷ for cyclopropane formation involving phosphorus ylides, as functionalised cyclopropanes are formed in a highly diastereoselective manner in excellent yields. We are currently evaluating the reactions of various 1,2-dioxines, alkyl hydroperoxides and disulfides with a variety of stabilised and non-stabilised ylides (phosphorus, sulfur *etc.*) and full mechanistic details will be presented in due course.



Scheme 1

Financial support in the form of set-up grants (Adelaide and Monash Universities, D. K. T.) and the ARC (E. R. T. T.) is greatly acknowledged. Assistance from Dr S. M. Pyke (Adelaide) in NMR spectral analysis is also acknowledged while Dr P. Perlmutter (Monash University) is thanked for co-supervision of T. J. R.

Notes and References

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† All new compounds have been fully characterised by elemental analysis, spectroscopy and mass spectrometry.

‡ Crystal data: $\text{C}_{20}\text{H}_{20}\text{O}_3$, triclinic, space group $P\bar{1}$ with $a = 7.952(3)$, $b = 18.417(4)$, $c = 5.680(2)$ Å, $\alpha = 90.51(2)$, $\beta = 92.28(3)$, $\gamma = 85.25(3)^\circ$, $U = 828.4(4)$ Å³, $Z = 2$, $D_c = 1.236$ g cm⁻³ and $\mu = 0.82$ cm⁻¹. Single-crystal X-ray diffraction data were collected at 293 K on a Rigaku AFC6R diffractometer (Mo-K α radiation) with $\theta/2\theta$ scans, $3 < \theta < 27.5^\circ$. The structure was solved with SIR92 and refined with the TEXSAN Structure Analysis Package (Molecular Structure Corporation, 1985) of crystallographic programs. A total of 937 reflections with $I \geq 3.0\sigma(I)$ were used in the refinement which converged with $R = 0.063$ and $R_w = 0.050 \{1/[\sigma^2(F) + 0.006F^2]\}$. CCDC 182/708.

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trans*-(±)-2-Carboxymethyl-3-phenylcyclopropane-1-carboxylic acid*Thomas D. Avery, Dennis K.
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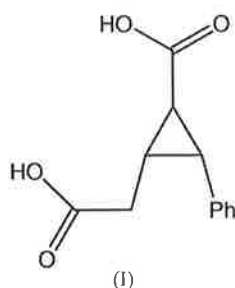
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Online 12 April 2001

The carboxyl and carboxymethyl substituents in the title compound, $C_{12}H_{12}O_4$, lie on opposite sides of the cyclopropyl ring and each carboxyl group participates in a centrosymmetric hydrogen-bonding scheme, typical for carboxylic acids, leading to the formation of zigzag chains in the crystal.

Comment

The title compound, (I), was prepared by the controlled hydrolysis of the parent methyl diester (Avery *et al.*, 2001). The structure determination confirms the overall stereochemistry, notably the positioning of the substituents around the cyclopropyl ring as shown in Fig. 1. The plane of the C11/O11/O11A carboxylic acid group is almost orthogonal to the cyclopropane plane, as seen in the value of the $X-C1-C11-O11$ torsion angle of $4.1(2)^\circ$, where X is the midpoint of the C2—C3 bond. By contrast, the dihedral angle formed by the planes of the phenyl and cyclopropyl rings is $68.70(11)^\circ$. The conformation is thus described as *cis*-bisected in accord with Allen (1980). The distal C2—C3 bond distance of $1.5027(19)$ Å is shorter, as expected (Allen, 1980), than the respective vicinal C1—C2 and C1—C3 bond distances of $1.5196(19)$ and $1.5195(17)$ Å, reflecting the influence of the π -acceptor carboxylic acid group upon the C—C bonds within the cyclopropyl ring.



Molecules associate in the lattice *via* hydrogen-bonding interactions involving both carboxylic acid residues so that each carboxylic acid group associates with its centrosymmetrically related mate. Thus, $O-H11A = 0.92$ Å, $H11A \cdots O11^i = 1.74$ Å and $O11A \cdots O11^i = 2.653(2)$ Å, and the angle at $H11A = 174^\circ$ [symmetry code: (i) $1 - x, -1 - y, -z$]. The comparable parameters for $H22A$ and $O22^{ii}$ are $0.87, 1.78$ and $2.646(2)$ Å, and 175° [symmetry code: (ii) $2 - x, -y, -z$]. Such association leads to the formation of zigzag chains extending in the *ab* plane.

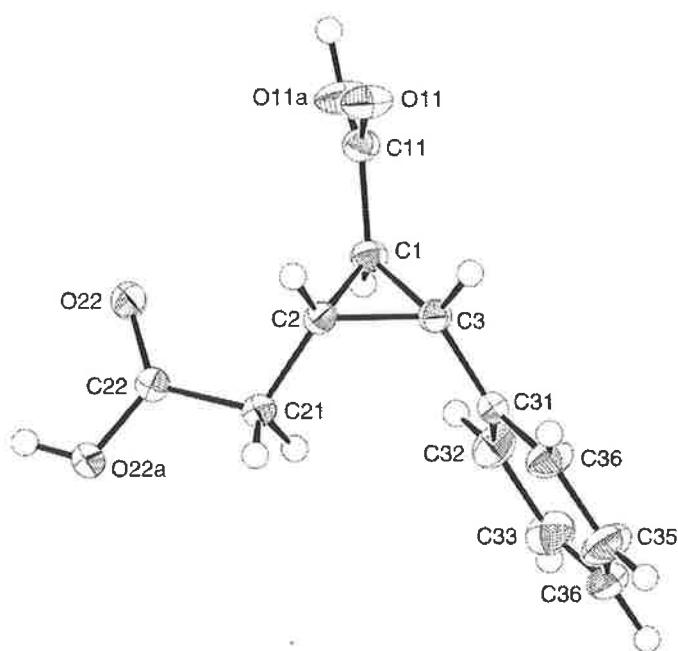


Figure 1
The molecular structure and crystallographic numbering scheme for (I). Displacement ellipsoids are shown at the 50% probability level (Johnson, 1976).

Experimental

The title compound was prepared according to the literature procedure of Avery *et al.* (2001). Colourless crystals were obtained by slow evaporation of a dichloromethane/heptane solution of the compound (m.p. 458–460 K).

Crystal data

$C_{12}H_{12}O_4$
 $M_r = 220.22$
Monoclinic, $P2_1/n$
 $a = 8.555$ (4) Å
 $b = 8.814$ (4) Å
 $c = 14.849$ (2) Å
 $\beta = 101.70$ (2)°
 $V = 1096.5$ (6) Å³
 $Z = 4$
 $D_x = 1.334$ Mg m⁻³

Mo $K\alpha$ radiation
Cell parameters from 24 reflections
 $\theta = 7.3$ – 10.7°
 $\mu = 0.10$ mm⁻¹
 $T = 173$ K
Block, colourless
 $0.45 \times 0.29 \times 0.16$ mm

Data collection

Rigaku AFC-7R diffractometer
 ω -2 θ scans
4704 measured reflections
2510 independent reflections
1829 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.020$
 $\theta_{max} = 27.5^\circ$

$h = -11 \rightarrow 6$
 $k = 0 \rightarrow 11$
 $l = -19 \rightarrow 19$
3 standard reflections
every 400 reflections
intensity decay: 0.3%

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.037$
 $wR(F^2) = 0.114$
 $S = 0.90$
2510 reflections
146 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0728P)^2 + 0.3498P]$
where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{max} < 0.001$
 $\Delta\rho_{max} = 0.21$ e Å⁻³
 $\Delta\rho_{min} = -0.23$ e Å⁻³

The C-bound H atoms were placed in geometrically calculated positions and included in the final refinement in the riding-model approximation with an overall isotropic displacement parameter. The H atoms on O atoms were located from a difference map but were not refined.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1996); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN* (Molecular Structure Corporation, 1997); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); software used to prepare material for publication: *SHELXL97* (Sheldrick, 1997).

The Australian Research Council is thanked for support.

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(±)-(3a*R*,4*R*,4a*S*)-4-Phenyl-3,3a,4,4a-tetrahydro-1*H*-cyclopropa[*c*]furan-1-one**Thomas D. Avery, Dennis K.
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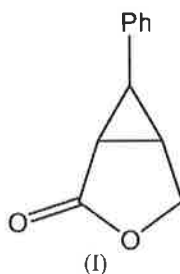
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The furanone ring in the title compound, $C_{11}H_{10}O_2$, is effectively planar and forms a dihedral angle of $74.42(14)^\circ$ with the cyclopropyl ring. The phenyl ring is somewhat twisted with respect to the approximate 'mirror plane' of the bicyclic system; the dihedral angles formed by the plane of the phenyl ring with the cyclopropyl and furanone mean planes are almost equal, *viz.* $98.30(14)$ and $98.14(10)^\circ$, respectively.

Comment

The title compound, (I), was prepared by the cyclization of 2-(hydroxymethyl)-3-phenylcyclopropane-1-carboxylic acid (Avery *et al.*, 2001). An enantiomerically pure form of the compound has been reported previously (Doyle *et al.*, 1995); the structure of the racemic crystal was determined in the present work (a view of the molecule with the atomic numbering is given in Fig. 1).



The deviations of the O2, C1, C3, C3a and C4a atoms from their least-squares plane are 0.080 (1), $-0.056(2)$, $-0.068(2)$, 0.035 (2) and 0.009 (2) Å, respectively; for reference, the displacement of the C4 atom from this plane is 1.285 (2) Å. The dihedral angle formed by the five-membered ring and the plane through the cyclopropyl ring is $74.42(14)^\circ$. The phenyl ring is somewhat twisted with respect to the approximate 'mirror plane' of the bicyclic system; the dihedral angles formed by the plane of the phenyl ring with the cyclopropyl and furanone mean planes are, quite expectedly, almost equal [$98.30(14)$ and $98.14(10)^\circ$, respectively], and the C4a—C4—C41—C42 torsion angle is $152.59(17)^\circ$. The twist about the C4—C41 bond presumably allows for the minimization of the total energy associated with short intramolecular H...H contacts involving H atoms at the C4, C3a, C4a, C42 and C46 atoms.

Experimental

The title compound was prepared by the trifluoroacetic acid-catalysed cyclization of the 2-(hydroxymethyl)-3-phenylcyclopropane-1-carboxylic acid precursor as described previously (Avery *et al.*, 2001).

Key indicators

Single-crystal X-ray study

 $T = 173$ KMean $\sigma(C-C) = 0.003$ Å R factor = 0.039 wR factor = 0.144

Data-to-parameter ratio = 16.6

For details of how these key indicators were automatically derived from the article, see <http://journals.iucr.org/e>.

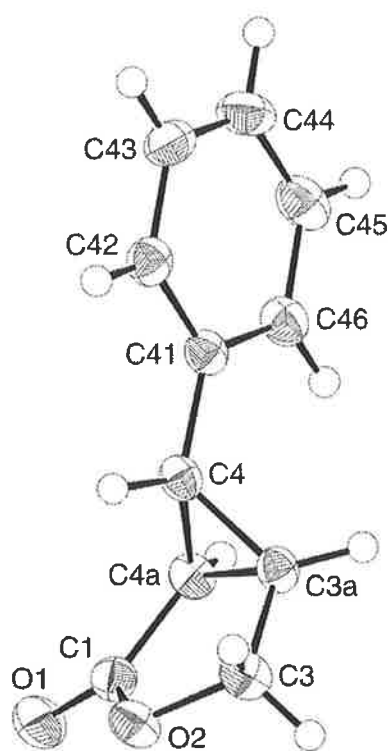


Figure 1
The molecular structure and crystallographic numbering scheme for (I). Displacement ellipsoids are shown at the 50% probability level (Johnson, 1976).

Crystals were obtained from the slow evaporation of a heptane solution of the compound; m.p. 367–369 K.

Crystal data

$C_{11}H_{10}O_2$
 $M_r = 174.20$
Monoclinic, $P2_1/n$
 $a = 8.927(1) \text{ \AA}$
 $b = 10.2311(9) \text{ \AA}$
 $c = 9.776(2) \text{ \AA}$
 $\beta = 106.04(2)^\circ$
 $V = 858.1(2) \text{ \AA}^3$
 $Z = 4$

$D_x = 1.348 \text{ Mg m}^{-3}$
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
 $\theta = 7.4\text{--}12.9^\circ$
 $\mu = 0.09 \text{ mm}^{-1}$
 $T = 173 \text{ K}$
Plate, pale yellow
 $0.45 \times 0.39 \times 0.07 \text{ mm}$

Data collection

Rigaku AFC-7R diffractometer
 ω - 2θ scans
2215 measured reflections
1975 independent reflections
1205 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.023$
 $\theta_{\text{max}} = 27.5^\circ$

$h = 0 \rightarrow 11$
 $k = 0 \rightarrow 13$
 $l = -12 \rightarrow 12$
3 standard reflections
every 400 reflections
intensity decay: 0.8%

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.039$
 $wR(F^2) = 0.144$
 $S = 0.93$
1975 reflections
119 parameters

H-atom parameters constrained
 $w = 1/[\sigma^2(F_o^2) + (0.1P)^2]$
where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\text{max}} < 0.001$
 $\Delta\rho_{\text{max}} = 0.23 \text{ e \AA}^{-3}$
 $\Delta\rho_{\text{min}} = -0.23 \text{ e \AA}^{-3}$

H atoms were placed in geometrically calculated positions and included in the final refinement in the riding model approximation with an overall displacement parameter.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1996); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *TEXSAN for Windows* (Molecular Structure Corporation, 1997); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); software used to prepare material for publication: *SHELXL97*.

The Australian Research Council is thanked for support.

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- Sheldrick, G. M. (1997). *SHELXL97*. University of Göttingen, Germany.

Crystal structure of *tert*-butyl 2-(2-oxo-2-phenylethyl)-3-phenylcyclopropane carboxylate, C₂₂H₂₄O₃

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Abstract

C₂₂H₂₄O₃, triclinic, $P\bar{1}$ (No. 2), $a = 6.0591(3)$ Å, $b = 15.2931(9)$ Å, $c = 20.501(1)$ Å, $\alpha = 98.598(2)^\circ$, $\beta = 97.471(3)^\circ$, $\gamma = 96.224(3)^\circ$, $V = 1846.5$ Å³, $Z = 4$, $R_{\text{gt}}(F) = 0.057$, $wR_{\text{ref}}(F) = 0.048$, $T = 173$ K.

Source of material

The compound was prepared as in [1] and recrystallised from an heptane solution as colorless crystals; mp 343 K – 345 K.

Discussion

The structure is one of three isomers isolated from the reaction of 3,6-diphenyl-1,2-dioxine with *t*-butyl stabilised phosphorus ylide [1]. In this isomer the phenyl group occupies a position opposite to the other substituents. There are two independent molecules in the asymmetric unit that differ from each other in the relative orientations of the substituents. The major disparity is found with the orientation of the phenyl groups as best exemplified in the C(1)/C(3)/C(31)/C(32) and C(1)/C(3)/C(31)/C(36) torsion angles of 124.4(2)° and 50.7(3)° for molecule a and –3.7(4)° and 175.2(2)° for molecule b.

Table 1. Data collection and handling.

Crystal:	colourless block, size 0.12 × 0.12 × 0.20 mm
Wavelength:	Mo K_α radiation (0.7107 Å)
μ :	0.79 cm ^{−1}
Diffractometer, scan mode:	Nonius Kappa CCD, $\omega/2\theta$
$2\theta_{\text{max}}$:	55.06°
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$:	8330, 8330
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 3 \sigma(I_{\text{obs}})$, 3955
$N(\text{param})_{\text{refined}}$:	451
Programs:	teXsan [2], SIR97 [3]

Table 2. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(1a)	2i	−0.3821	−0.3087	0.3911	0.034
H(1b)	2i	−0.3946	0.2035	−0.1036	0.033
H(2a)	2i	−0.3192	−0.3839	0.4791	0.037
H(2b)	2i	−0.3015	0.1152	−0.0237	0.033
H(3a)	2i	0.0288	−0.3843	0.3994	0.036
H(3b)	2i	−0.0095	0.1163	−0.1206	0.032
H(14a)	2i	−0.6318	−0.5399	0.2282	0.049
H(14b)	2i	−0.8052	−0.5340	0.1668	0.049
H(14c)	2i	−0.8621	−0.5088	0.2383	0.049
H(14d)	2i	−0.6616	0.0940	−0.3743	0.048

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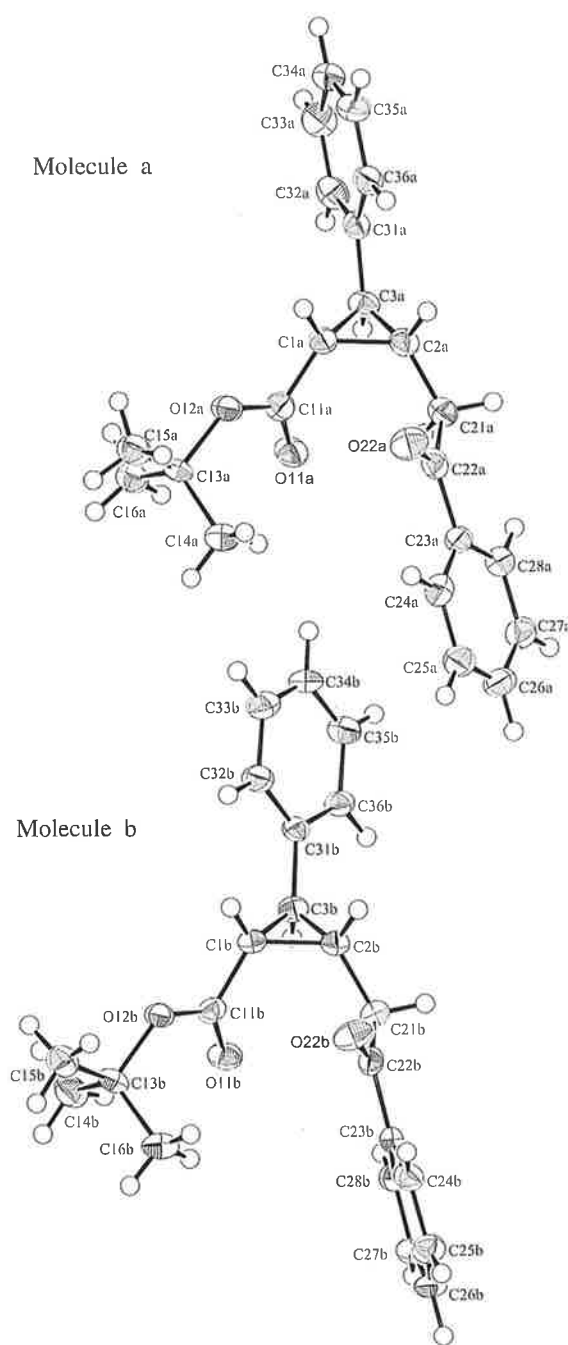


Table 2. Continued.

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(14e)	2i	−0.5282	0.1793	−0.3300	0.048
H(14f)	2i	−0.4533	0.0867	−0.3237	0.048
H(15a)	2i	−0.7729	−0.2939	0.2176	0.047
H(15b)	2i	−0.8919	−0.3637	0.1570	0.047
H(15c)	2i	−0.9466	−0.3710	0.2280	0.047
H(15d)	2i	−0.8429	0.2266	−0.2881	0.046
H(15e)	2i	−1.0191	0.1455	−0.3209	0.046
H(15f)	2i	−0.9768	0.1734	−0.2439	0.046
H(16a)	2i	−0.3751	−0.4424	0.1698	0.045
H(16b)	2i	−0.4098	−0.3431	0.1719	0.045
H(16c)	2i	−0.5620	−0.4164	0.1199	0.045
H(16d)	2i	−0.7147	−0.0252	−0.2803	0.045
H(16e)	2i	−0.9347	−0.0066	−0.3206	0.045
H(16f)	2i	−0.9050	0.0082	−0.2432	0.045
H(21a)	2i	−0.1943	−0.5271	0.3950	0.040
H(21b)	2i	−0.2311	−0.5280	0.4684	0.040
H(21c)	2i	−0.2448	−0.0233	−0.1245	0.036
H(21d)	2i	−0.2336	−0.0311	−0.0496	0.036
H(24a)	2i	−0.8948	−0.6494	0.3395	0.040

Table 2. Continued.

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(24b)	2i	−0.9280	−0.1500	−0.0992	0.036
H(25a)	2i	−0.9712	−0.8013	0.2968	0.045
H(25b)	2i	−1.0459	−0.2970	−0.1487	0.041
H(26a)	2i	−0.6927	−0.8935	0.3100	0.046
H(26b)	2i	−0.8192	−0.3743	−0.2149	0.039
H(27a)	2i	−0.3366	−0.8343	0.3673	0.045
H(27b)	2i	−0.4719	−0.3040	−0.2285	0.040
H(28a)	2i	−0.2586	−0.6820	0.4095	0.040
H(28b)	2i	−0.3475	−0.1582	−0.1759	0.035
H(32a)	2i	0.3111	−0.2548	0.4201	0.045
H(32b)	2i	−0.1770	0.3168	−0.0470	0.043
H(33b)	2i	0.0518	0.4336	0.0249	0.051
H(33a)	2i	0.4503	−0.1099	0.4696	0.051
H(34a)	2i	0.2413	−0.0265	0.5374	0.048
H(34b)	2i	0.4167	0.4161	0.0678	0.046
H(35a)	2i	−0.1031	−0.0923	0.5578	0.045
H(35b)	2i	0.5468	0.2796	0.0422	0.041
H(36a)	2i	−0.2385	−0.2384	0.5107	0.039
H(36b)	2i	0.3175	0.1622	−0.0281	0.035

Table 3. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
O(11a)	2i	−0.2785(2)	−0.47050(9)	0.28856(6)	0.0452(9)	0.035(1)	0.0316(9)	0.0162(8)	0.0051(7)	−0.0020(7)
O(11b)	2i	−0.3424(2)	0.04664(9)	−0.21917(6)	0.0361(8)	0.0314(9)	0.0313(9)	0.0077(7)	0.0066(7)	−0.0050(7)
O(12a)	2i	−0.5357(2)	−0.37305(8)	0.28155(6)	0.0318(8)	0.0268(9)	0.0300(9)	0.0041(7)	−0.0018(7)	−0.0017(7)
O(12b)	2i	−0.6016(2)	0.14290(8)	−0.21135(6)	0.0279(8)	0.0246(8)	0.0252(8)	0.0024(7)	−0.0006(7)	−0.0014(7)
O(22a)	2i	−0.6793(2)	−0.50791(9)	0.40593(7)	0.0396(9)	0.037(1)	0.051(1)	0.0106(8)	0.0102(8)	0.0019(8)
O(22b)	2i	−0.6941(2)	0.00030(9)	−0.07775(7)	0.0364(8)	0.0278(9)	0.052(1)	0.0050(7)	0.0128(8)	−0.0021(8)
C(1a)	2i	−0.3078(3)	−0.3598(1)	0.3819(1)	0.034(1)	0.024(1)	0.028(1)	0.010(1)	0.004(1)	0.002(1)
C(1b)	2i	−0.3323(3)	0.1512(1)	−0.1190(1)	0.033(1)	0.021(1)	0.026(1)	0.004(1)	0.004(1)	−0.001(1)
C(2a)	2i	−0.2656(3)	−0.4089(1)	0.4398(1)	0.036(1)	0.030(1)	0.027(1)	0.008(1)	0.006(1)	0.001(1)
C(2b)	2i	−0.2725(3)	0.0930(1)	−0.06711(9)	0.032(1)	0.024(1)	0.024(1)	0.003(1)	0.003(1)	−0.001(1)
C(3a)	2i	−0.0743(3)	−0.3524(1)	0.42131(9)	0.030(1)	0.030(1)	0.029(1)	0.008(1)	0.004(1)	−0.002(1)
C(3b)	2i	−0.0907(3)	0.1490(1)	−0.09089(9)	0.028(1)	0.024(1)	0.027(1)	0.005(1)	0.007(1)	−0.000(1)
C(11a)	2i	−0.3671(3)	−0.4084(1)	0.3129(1)	0.029(1)	0.030(1)	0.029(1)	0.004(1)	0.004(1)	0.005(1)
C(11b)	2i	−0.4201(3)	0.1068(1)	−0.1882(1)	0.028(1)	0.022(1)	0.030(1)	−0.002(1)	0.006(1)	0.004(1)
C(13a)	2i	−0.6469(3)	−0.4120(1)	0.21306(9)	0.029(1)	0.028(1)	0.024(1)	−0.002(1)	−0.004(1)	−0.002(1)
C(13b)	2i	−0.7284(3)	0.1078(1)	−0.27842(9)	0.028(1)	0.033(1)	0.022(1)	−0.001(1)	−0.001(1)	−0.002(1)
C(14a)	2i	−0.7457(3)	−0.5076(1)	0.2114(1)	0.044(1)	0.033(2)	0.039(1)	−0.005(1)	−0.001(1)	−0.000(1)
C(14b)	2i	−0.5789(3)	0.1179(1)	−0.3316(1)	0.044(1)	0.045(2)	0.028(1)	0.002(1)	0.005(1)	0.004(1)
C(15a)	2i	−0.8316(3)	−0.3549(1)	0.2030(1)	0.038(1)	0.039(2)	0.037(1)	0.002(1)	0.000(1)	0.002(1)
C(15b)	2i	−0.9086(3)	0.1690(1)	−0.2833(1)	0.035(1)	0.041(2)	0.037(1)	0.004(1)	−0.003(1)	0.005(1)
C(16a)	2i	−0.4833(3)	−0.4026(1)	0.1642(1)	0.039(1)	0.037(2)	0.033(1)	−0.001(1)	0.001(1)	0.001(1)
C(16b)	2i	−0.8302(3)	0.0121(1)	−0.2809(1)	0.037(1)	0.031(1)	0.039(1)	−0.004(1)	0.002(1)	−0.004(1)
C(21a)	2i	−0.2844(3)	−0.5088(1)	0.42791(9)	0.037(1)	0.035(2)	0.027(1)	0.004(1)	0.004(1)	0.002(1)
C(21b)	2i	−0.3078(3)	−0.0068(1)	−0.08508(9)	0.034(1)	0.023(1)	0.031(1)	0.001(1)	0.003(1)	0.003(1)
C(22a)	2i	−0.5242(3)	−0.5524(1)	0.40411(9)	0.038(1)	0.035(2)	0.023(1)	0.007(1)	0.009(1)	0.006(1)
C(22b)	2i	−0.5533(3)	−0.0449(1)	−0.09721(9)	0.033(1)	0.025(1)	0.025(1)	0.005(1)	0.006(1)	0.008(1)
C(23a)	2i	−0.5678(3)	−0.6503(1)	0.37851(9)	0.037(1)	0.026(1)	0.025(1)	0.004(1)	0.008(1)	0.003(1)
C(23b)	2i	−0.6235(3)	−0.1390(1)	−0.13165(9)	0.028(1)	0.022(1)	0.022(1)	0.003(1)	−0.000(1)	0.005(1)
C(24a)	2i	−0.7805(3)	−0.6867(1)	0.3450(1)	0.034(1)	0.034(2)	0.036(1)	0.008(1)	0.012(1)	0.009(1)
C(24b)	2i	−0.8332(3)	−0.1815(1)	−0.12483(9)	0.029(1)	0.030(1)	0.029(1)	0.006(1)	0.000(1)	0.002(1)
C(25a)	2i	−0.8260(3)	−0.7770(2)	0.3197(1)	0.039(1)	0.037(2)	0.035(1)	−0.003(1)	0.007(1)	0.005(1)
C(25b)	2i	−0.9045(3)	−0.2685(1)	−0.1548(1)	0.029(1)	0.032(1)	0.039(1)	−0.003(1)	0.002(1)	0.005(1)
C(26a)	2i	−0.6611(4)	−0.8317(1)	0.3277(1)	0.051(2)	0.027(1)	0.038(2)	−0.000(1)	0.014(1)	0.004(1)
C(26b)	2i	−0.7698(3)	−0.3145(1)	−0.1938(1)	0.036(1)	0.023(1)	0.033(1)	−0.003(1)	−0.000(1)	−0.004(1)
C(27a)	2i	−0.4498(4)	−0.7966(1)	0.3614(1)	0.046(1)	0.032(2)	0.036(1)	0.010(1)	0.009(1)	0.006(1)
C(27b)	2i	−0.5641(3)	−0.2728(1)	−0.2016(1)	0.043(1)	0.027(1)	0.030(1)	0.007(1)	0.007(1)	−0.002(1)
C(28a)	2i	−0.4039(3)	−0.7060(1)	0.3865(1)	0.036(1)	0.032(2)	0.030(1)	0.003(1)	0.005(1)	0.005(1)
C(28b)	2i	−0.4905(3)	−0.1859(1)	−0.17051(9)	0.032(1)	0.027(1)	0.027(1)	0.002(1)	0.005(1)	0.004(1)
C(31a)	2i	0.0198(3)	−0.2623(1)	0.45860(9)	0.029(1)	0.031(1)	0.025(1)	0.005(1)	0.001(1)	0.005(1)
C(31b)	2i	0.0478(3)	0.2273(1)	−0.04560(9)	0.030(1)	0.024(1)	0.020(1)	0.001(1)	0.006(1)	0.002(1)
C(32a)	2i	0.2251(3)	−0.2220(2)	0.4482(1)	0.036(1)	0.045(2)	0.031(1)	0.009(1)	0.006(1)	0.003(1)
C(32b)	2i	−0.0294(3)	0.3087(1)	−0.0290(1)	0.037(1)	0.030(1)	0.036(1)	0.007(1)	−0.008(1)	−0.001(1)
C(33a)	2i	0.3083(3)	−0.1356(2)	0.4774(1)	0.035(1)	0.049(2)	0.041(2)	−0.007(1)	0.009(1)	0.007(1)
C(33b)	2i	0.1070(4)	0.3784(1)	0.0136(1)	0.053(2)	0.026(1)	0.043(2)	0.009(1)	−0.004(1)	−0.003(1)

Table 3. Continued.

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
C(34a)	2i	0.1860(4)	−0.0865(1)	0.5179(1)	0.047(1)	0.034(2)	0.033(1)	−0.005(1)	−0.001(1)	0.001(1)
C(34b)	2i	0.3224(4)	0.3679(1)	0.0395(1)	0.050(2)	0.025(1)	0.033(1)	−0.003(1)	−0.003(1)	−0.006(1)
C(35a)	2i	−0.0181(3)	−0.1255(1)	0.5297(1)	0.045(1)	0.033(2)	0.032(1)	0.005(1)	0.006(1)	−0.004(1)
C(35b)	2i	0.3993(3)	0.2875(1)	0.0241(1)	0.032(1)	0.034(2)	0.034(1)	0.002(1)	0.001(1)	−0.000(1)
C(36a)	2i	−0.0993(3)	−0.2122(1)	0.5013(1)	0.033(1)	0.034(2)	0.030(1)	0.002(1)	0.003(1)	0.004(1)
C(36b)	2i	0.2626(3)	0.2178(1)	−0.0180(1)	0.032(1)	0.023(1)	0.030(1)	0.004(1)	0.004(1)	−0.001(1)

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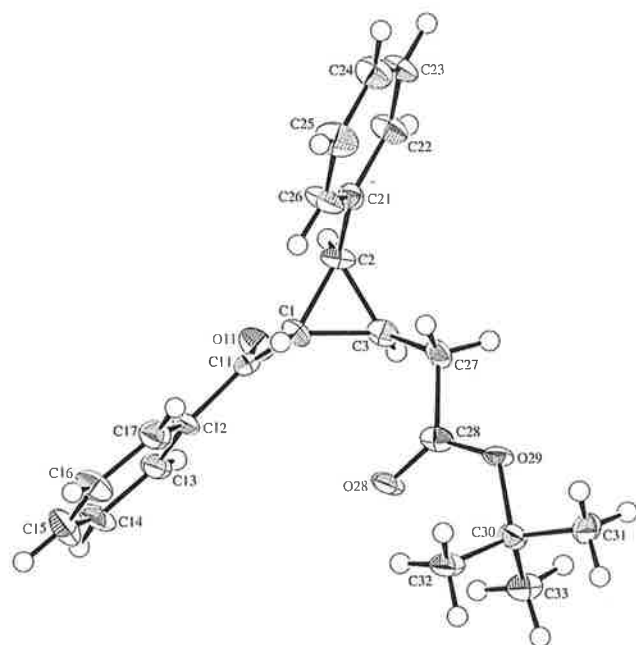
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Crystal structure of *tert*-butyl 2-(2-benzoyl-3-phenylcyclopropyl)acetate, $C_{22}H_{24}O_3$

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Abstract

$C_{22}H_{24}O_3$, orthorhombic, $P2_12_12_1$ (No. 19), $a = 5.8623(4)$ Å, $b = 8.5835(4)$ Å, $c = 35.864(2)$ Å, $V = 1804.6$ Å³, $Z = 4$, $R_{gt}(F) = 0.041$, $wR_{ref}(F) = 0.036$, $T = 173$ K.

Source of material

The compound was prepared as in [1] and recrystallised from an heptane solution as colorless crystals; mp 373 K – 374 K.

Discussion

The *trans* disposition of the benzoyl group with respect to the remaining non-H substituents about the cyclopropane ring is consistent with related systems [1–5].

Table 1. Data collection and handling.

Crystal:	colourless block, size $0.20 \times 0.10 \times 0.10$ mm
Wavelength:	Mo $K\alpha$ radiation (0.7107 Å)
μ :	0.81 cm^{-1}
Diffraction, scan mode:	Nonius Kappa CCD, $\omega/2\theta$
$2\theta_{\text{max}}$:	55.24°
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$:	6204, 3566
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 3 \sigma(I_{\text{obs}})$, 1156
$N(\text{param})_{\text{refined}}$:	226
Programs:	SIR92 [6], teXsan [7]

Table 2. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(1)	4a	−0.1383	0.1106	0.6236	0.026
H(2)	4a	0.2006	0.1346	0.5667	0.031
H(3)	4a	0.1128	0.3682	0.5931	0.029
H(13)	4a	0.4948	0.1897	0.6936	0.032
H(14)	4a	0.4845	0.1216	0.7555	0.044
H(15)	4a	0.1754	−0.0162	0.7798	0.047
H(16)	4a	−0.1372	−0.0719	0.7413	0.044
H(17)	4a	−0.1359	0.0063	0.6789	0.035
H(22)	4a	0.0783	0.1154	0.5004	0.039
H(23)	4a	−0.1461	−0.0137	0.4572	0.044
H(24)	4a	−0.4710	−0.1457	0.4757	0.041
H(25)	4a	−0.5846	−0.1388	0.5383	0.050
H(26)	4a	−0.3487	−0.0143	0.5822	0.044
H(27a)	4a	−0.2283	0.4517	0.5660	0.030
H(27b)	4a	−0.3496	0.2998	0.5786	0.030
H(31a)	4a	−0.8899	0.6583	0.6067	0.038
H(31b)	4a	−0.8838	0.7952	0.6349	0.038
H(31c)	4a	−0.7252	0.7972	0.6003	0.038
H(32a)	4a	−0.6011	0.4885	0.6823	0.035
H(32b)	4a	−0.7853	0.6152	0.6891	0.035
H(32c)	4a	−0.8287	0.4837	0.6603	0.035
H(33a)	4a	−0.3671	0.8169	0.6358	0.038
H(33b)	4a	−0.5089	0.8345	0.6721	0.038
H(33c)	4a	−0.3228	0.7065	0.6693	0.038

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Table 3. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	x	y	z	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
O(11)	4a	0.3966(7)	0.1721(4)	0.6263(1)	0.022(3)	0.045(3)	0.024(3)	-0.004(2)	0.002(2)	0.003(2)
O(28)	4a	-0.2449(7)	0.4413(4)	0.6509(1)	0.031(3)	0.038(2)	0.013(3)	0.004(2)	-0.003(2)	-0.007(2)
O(29)	4a	-0.5043(6)	0.5508(4)	0.61188(9)	0.019(3)	0.032(2)	0.015(2)	0.007(2)	0.001(2)	-0.007(2)
C(1)	4a	0.000(1)	0.1532(5)	0.6144(2)	0.017(4)	0.031(3)	0.017(4)	-0.005(3)	-0.004(4)	0.002(3)
C(2)	4a	0.044(1)	0.1454(6)	0.5729(2)	0.025(5)	0.034(4)	0.018(4)	-0.001(3)	0.001(4)	-0.010(3)
C(3)	4a	-0.013(1)	0.2990(6)	0.5905(1)	0.020(4)	0.030(4)	0.021(4)	-0.005(3)	0.005(4)	-0.000(3)
C(11)	4a	0.207(1)	0.1441(6)	0.6387(2)	0.036(5)	0.016(3)	0.021(4)	0.004(4)	0.002(4)	-0.003(3)
C(12)	4a	0.184(1)	0.1041(5)	0.6794(2)	0.026(5)	0.028(4)	0.011(4)	0.004(3)	0.000(4)	-0.001(3)
C(13)	4a	0.365(1)	0.1370(6)	0.7031(2)	0.030(5)	0.032(3)	0.019(4)	0.002(3)	-0.001(4)	-0.005(3)
C(14)	4a	0.360(1)	0.0953(7)	0.7398(2)	0.036(5)	0.057(5)	0.016(5)	0.008(4)	-0.010(4)	-0.008(3)
C(15)	4a	0.176(1)	0.0155(7)	0.7544(2)	0.037(6)	0.057(5)	0.022(4)	0.009(4)	0.002(4)	0.012(3)
C(16)	4a	-0.009(1)	-0.0178(6)	0.7315(2)	0.038(5)	0.053(4)	0.020(4)	-0.003(4)	0.009(4)	0.002(3)
C(17)	4a	-0.007(1)	0.0274(6)	0.6943(2)	0.029(5)	0.035(4)	0.025(4)	0.003(4)	-0.003(4)	-0.004(3)
C(21)	4a	-0.113(1)	0.0653(6)	0.5462(2)	0.021(4)	0.026(3)	0.019(4)	0.006(3)	-0.001(3)	0.001(3)
C(22)	4a	-0.0551(9)	0.0630(6)	0.5086(2)	0.034(5)	0.044(4)	0.021(4)	-0.009(4)	0.005(4)	-0.001(3)
C(23)	4a	-0.189(1)	-0.0140(7)	0.4827(2)	0.051(5)	0.046(4)	0.014(4)	0.004(4)	0.000(4)	-0.002(3)
C(24)	4a	-0.382(1)	-0.0912(6)	0.4935(2)	0.030(5)	0.041(5)	0.030(5)	-0.011(3)	-0.004(4)	-0.002(3)
C(25)	4a	-0.447(1)	-0.0893(6)	0.5306(2)	0.034(5)	0.058(5)	0.034(5)	-0.009(4)	0.013(4)	-0.003(3)
C(26)	4a	-0.308(1)	-0.0121(7)	0.5566(2)	0.046(5)	0.048(4)	0.015(4)	-0.015(4)	0.001(4)	-0.005(3)
C(27)	4a	-0.241(1)	0.3768(5)	0.5854(2)	0.030(5)	0.027(4)	0.017(4)	-0.003(3)	0.004(4)	0.006(3)
C(28)	4a	-0.325(1)	0.4580(7)	0.6204(2)	0.021(5)	0.028(4)	0.021(5)	-0.010(3)	0.010(4)	-0.003(4)
C(30)	4a	-0.611(1)	0.6492(7)	0.6407(2)	0.025(4)	0.028(4)	0.017(4)	0.001(3)	0.002(3)	0.000(3)
C(31)	4a	-0.795(1)	0.7327(5)	0.6185(2)	0.034(4)	0.029(3)	0.033(4)	0.014(3)	-0.010(4)	-0.004(3)
C(32)	4a	-0.7164(9)	0.5499(6)	0.6709(1)	0.029(4)	0.035(3)	0.024(4)	0.003(4)	-0.005(4)	-0.012(3)
C(33)	4a	-0.4360(9)	0.7625(6)	0.6559(2)	0.032(5)	0.035(3)	0.031(4)	0.001(3)	-0.001(4)	-0.010(3)

Acknowledgment. The Australian Research Council is thanked for support.

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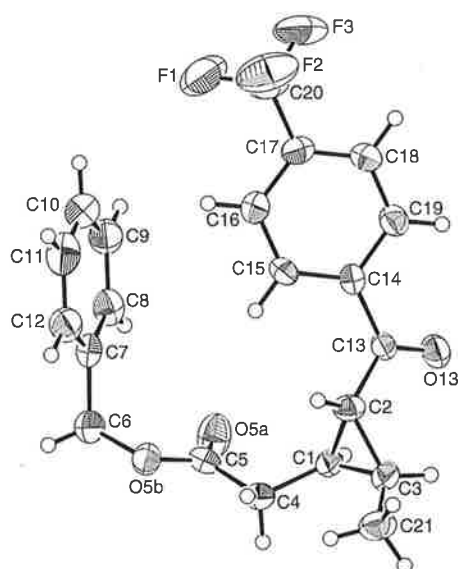
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Crystal structure of benzyl 2-(3-methyl-2-(*p*-trifluoromethylbenzoyl)-cyclopropyl)acetate, C₂₁H₁₉F₃O₃

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Abstract

C₂₁H₁₉F₃O₃, triclinic, *P* $\bar{1}$ (No. 2), *a* = 7.934(4) Å, *b* = 20.525(6) Å, *c* = 5.642(2) Å, α = 91.10(3)°, β = 91.58(4)°, γ = 87.29(3)°, *V* = 917.2 Å³, *Z* = 2, *R*_{gt}(*F*) = 0.066, *R*_w(*F*) = 0.064, *T* = 293 K.

Source of material

To a mixture of 3-methyl-6-[4-(trifluoromethyl)phenyl]-3,6-dihydro-1,2-dioxine (0.5 g) in dichloromethane (5 ml) under a nitrogen atmosphere at ambient temperature was added benzyl 1,2-(triphenylphosphoranylidene) acetate (0.9 g). After 2 days, the mixture was concentrated and subjected to column chromatography. Elution with a mixture of hexane/ethyl acetate (4:1) afforded the title compound in 82 % yield as a white solid. Recrystallisation from heptane gave colorless crystals; mp 364 K – 365 K.

Discussion

The substitution pattern about the cyclopropyl ring is as found in related systems [1–3].

Table 1. Data collection and handling.

Crystal:	colorless plate, size 0.05 x 0.29 x 0.45 mm
Wavelength:	Mo <i>K</i> α radiation (0.7107 Å)
μ :	1.10 cm ⁻¹
Diffractometer, scan mode:	Rigaku AFC6R, $\omega/2\theta$
$2\theta_{\max}$:	55°
<i>N</i> (<i>hkl</i>) _{measured} , <i>N</i> (<i>hkl</i>) _{unique} :	4457, 4159
Criterion for <i>I</i> _{obs} , <i>N</i> (<i>hkl</i>) _{gt} :	<i>I</i> _{obs} > 3 σ (<i>I</i> _{obs}), 1251
<i>N</i> (<i>param</i>) _{refined} :	244
Program:	TEXSAN [4]

Table 2. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(1)	2i	0.4773	0.0922	0.0838	0.0561
H(2)	2i	0.2462	0.1578	–0.2421	0.0603
H(3)	2i	0.2032	0.0652	0.1190	0.0675
H(4a)	2i	0.4417	0.0772	–0.4141	0.0674
H(4b)	2i	0.5499	0.0270	–0.2660	0.0674
H(6a)	2i	0.8738	0.1527	–0.7284	0.0780
H(6b)	2i	0.9283	0.1483	–0.4627	0.0780
H(8)	2i	0.9218	0.2448	–0.2253	0.0765
H(9)	2i	0.8692	0.3577	–0.1893	0.0882
H(10)	2i	0.7232	0.4131	–0.4915	0.0910
H(11)	2i	0.6214	0.3562	–0.8167	0.0976
H(12)	2i	0.6784	0.2433	–0.8536	0.0809
H(15)	2i	0.3830	0.2499	–0.2655	0.0622
H(16)	2i	0.3890	0.3597	–0.3604	0.0715
H(18)	2i	0.1294	0.4065	0.2301	0.0742
H(19)	2i	0.1308	0.2977	0.3282	0.0653
H(21a)	2i	0.2105	0.0284	–0.3641	0.0882
H(21b)	2i	0.0377	0.0523	–0.2641	0.0882
H(21c)	2i	0.1300	–0.0102	–0.1660	0.0882

Table 3. Atomic coordinates and displacement parameters (in Å²).

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
F(1)	2i	0.3825(8)	0.4790(3)	–0.264(1)	0.121(5)	0.073(4)	0.251(8)	–0.007(3)	0.060(5)	0.038(4)
F(2)	2i	0.1215(8)	0.4779(2)	–0.286(1)	0.136(5)	0.073(4)	0.208(7)	0.004(4)	–0.058(5)	0.032(4)
F(3)	2i	0.2390(8)	0.5045(2)	0.036(1)	0.217(7)	0.054(4)	0.162(6)	–0.018(4)	0.020(5)	–0.030(4)
O(5a)	2i	0.7517(7)	0.1284(3)	–0.140(1)	0.074(4)	0.119(5)	0.067(4)	–0.032(4)	0.000(3)	0.006(4)

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Table 3. Continued.

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
O(5b)	2i	0.6928(6)	0.1246(2)	−0.5257(9)	0.062(4)	0.059(3)	0.053(3)	−0.013(3)	0.009(3)	−0.001(3)
O(13)	2i	0.2476(6)	0.1769(2)	0.3123(9)	0.072(4)	0.065(4)	0.051(4)	0.006(3)	0.016(3)	0.004(3)
C(1)	2i	0.4134(9)	0.0907(3)	−0.061(1)	0.053(5)	0.039(4)	0.049(5)	0.004(4)	0.010(4)	0.011(3)
C(2)	2i	0.2714(8)	0.1430(3)	−0.086(1)	0.051(5)	0.038(5)	0.061(5)	0.006(4)	−0.001(4)	0.004(4)
C(3)	2i	0.2348(9)	0.0729(3)	−0.039(1)	0.060(6)	0.042(5)	0.067(6)	0.003(4)	0.019(4)	0.014(4)
C(4)	2i	0.5134(9)	0.0716(3)	−0.278(1)	0.058(5)	0.041(5)	0.069(5)	0.000(4)	−0.011(4)	0.000(4)
C(5)	2i	0.6655(9)	0.1113(3)	−0.305(2)	0.053(6)	0.044(5)	0.052(5)	0.007(4)	0.001(5)	−0.009(4)
C(6)	2i	0.8397(9)	0.1616(4)	−0.570(1)	0.056(5)	0.062(6)	0.078(6)	−0.006(5)	0.018(4)	0.000(5)
C(7)	2i	0.8036(9)	0.2340(4)	−0.540(1)	0.044(5)	0.063(6)	0.042(5)	−0.010(4)	0.004(4)	0.006(4)
C(8)	2i	0.8603(9)	0.2674(4)	−0.348(1)	0.049(5)	0.082(7)	0.060(6)	−0.016(5)	0.001(4)	−0.010(5)
C(9)	2i	0.830(1)	0.3347(5)	−0.326(2)	0.078(7)	0.075(7)	0.069(7)	−0.027(5)	0.008(5)	−0.017(6)
C(10)	2i	0.743(1)	0.3671(4)	−0.503(2)	0.084(7)	0.066(6)	0.079(7)	−0.008(5)	0.012(6)	0.006(6)
C(11)	2i	0.685(1)	0.3337(5)	−0.696(2)	0.063(6)	0.101(8)	0.079(7)	0.010(6)	0.003(5)	0.029(6)
C(12)	2i	0.717(1)	0.2664(4)	−0.717(1)	0.064(6)	0.071(7)	0.068(6)	−0.011(5)	0.005(5)	−0.005(5)
C(13)	2i	0.2578(8)	0.1930(3)	0.107(1)	0.045(5)	0.043(5)	0.041(5)	0.005(4)	0.009(4)	0.003(4)
C(14)	2i	0.2591(8)	0.2621(4)	0.039(1)	0.038(5)	0.054(5)	0.037(5)	−0.004(4)	0.002(4)	0.000(4)
C(15)	2i	0.3324(8)	0.2819(4)	−0.163(1)	0.053(5)	0.047(5)	0.055(5)	0.003(4)	0.013(4)	−0.010(4)
C(16)	2i	0.3351(9)	0.3470(4)	−0.221(1)	0.057(5)	0.059(6)	0.063(6)	−0.010(4)	0.012(4)	0.002(5)
C(17)	2i	0.2570(9)	0.3936(4)	−0.072(1)	0.050(5)	0.043(5)	0.072(6)	−0.003(4)	−0.002(4)	0.002(5)
C(18)	2i	0.1823(9)	0.3746(4)	0.129(1)	0.065(6)	0.050(6)	0.071(6)	−0.001(4)	0.015(5)	−0.012(5)
C(19)	2i	0.1826(8)	0.3101(4)	0.187(1)	0.049(5)	0.058(6)	0.056(5)	0.004(4)	0.008(4)	−0.001(5)
C(20)	2i	0.251(1)	0.4619(5)	−0.142(2)	0.097(9)	0.048(7)	0.12(1)	−0.005(6)	0.002(7)	0.002(6)
C(21)	2i	0.1448(9)	0.0320(4)	−0.226(1)	0.063(5)	0.050(5)	0.108(7)	−0.012(4)	0.009(5)	−0.009(5)

Acknowledgments. The Faculty of Science and the Australian Research Council are thanked for support.

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Crystal structure of benzyl 2-(2-benzoylcyclopropyl)acetate, C₁₉H₁₈O₃

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Table 1. Parameters used for the X-ray data collection

Crystal:	colorless plate, size 0.13 x 0.26 x 0.39 mm
Wavelength:	Mo K α radiation (0.7107 Å)
μ :	0.84 cm ⁻¹
Diffractometer:	Rigaku AFC6R
Scan mode:	$\omega/2\theta$
$T_{\text{measurement}}$:	293 K
$2\theta_{\text{max}}$:	55°
$N(hkl)_{\text{unique}}$:	1486
Criterion for I_o :	$I_o > 3 \sigma(I_o)$
$N(\text{param})_{\text{refined}}$:	199
Program:	TEXSAN

Table 2. Final atomic coordinates and displacement parameters (in Å²)

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(1)	4e	0.1971	-0.5613	0.2129	0.061
H(2)	4e	0.3623	-0.2478	0.1619	0.058
H(3a)	4e	0.5095	-0.3036	0.2223	0.077
H(3b)	4e	0.4996	-0.5751	0.2177	0.077
H(4a)	4e	0.1493	-0.2073	0.2483	0.062
H(4b)	4e	0.2302	-0.0649	0.2159	0.062
H(6a)	4e	-0.2929	-0.0104	0.1823	0.072
H(6b)	4e	-0.2406	0.2504	0.1764	0.072
H(8)	4e	-0.3235	-0.2629	0.1287	0.069
H(9)	4e	-0.3158	-0.3156	0.0634	0.084
H(10)	4e	-0.1740	-0.0415	0.0265	0.089
H(11)	4e	-0.0482	0.2884	0.0551	0.091
H(12)	4e	-0.0658	0.3483	0.1200	0.078
H(15)	4e	0.4459	-0.8609	0.0897	0.065
H(16)	4e	0.4186	-0.7960	0.0245	0.078
H(17)	4e	0.2832	-0.4606	0.0009	0.080
H(18)	4e	0.1737	-0.1849	0.0422	0.077
H(19)	4e	0.2117	-0.2370	0.1077	0.062

Source of material: To a mixture of 3-phenyl-3,6-dihydro-1,2-dioxine (0.6 g) in dichloromethane (5 ml) under a nitrogen atmosphere at ambient temperature was added benzyl 1,2-(triphenylphosphoranylidene)acetate (1.53 g). After 3 days the mixture was concentrated and subjected to column chromatography. Elution with a mixture of hexane/ethyl acetate (7:3) afforded the title compound in 83% yield as a white solid. Recrystallisation from an heptane solution gave colorless crystals with mp 317 K – 318 K.

The substituents occupy trans positions about the cyclopropyl ring and the conformation is almost identical to that found in the related structure with a methyl group at the C3 position (*cis* to C4); see ref. 1.

C₁₉H₁₈O₃, monoclinic, *P*2₁/*c*1 (No. 14), *a* = 7.786(5) Å, *b* = 5.675(2) Å, *c* = 35.254(3) Å, β = 92.34(3)°, *V* = 1556.4 Å³, *Z* = 4, *R*(*F*) = 0.055, *R*_w(*F*) = 0.054.

Table 3. Final atomic coordinates and displacement parameters (in Å²)

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
O(5)	4e	-0.1084(4)	-0.3336(5)	0.19549(9)	0.075(2)	0.053(2)	0.135(3)	-0.012(2)	-0.008(2)	0.014(2)
O(5a)	4e	-0.0445(3)	0.0466(4)	0.19246(7)	0.064(2)	0.044(2)	0.060(2)	0.006(1)	-0.003(1)	-0.004(1)
O(13)	4e	0.3706(4)	-0.8033(4)	0.15843(7)	0.095(2)	0.042(2)	0.066(2)	0.012(2)	0.021(1)	0.014(1)
C(1)	4e	0.2556(5)	-0.4167(6)	0.20921(9)	0.066(3)	0.043(2)	0.045(2)	0.004(2)	0.016(2)	0.011(2)
C(2)	4e	0.3553(5)	-0.3997(6)	0.17306(9)	0.063(3)	0.040(2)	0.044(2)	-0.004(2)	0.018(2)	0.005(2)
C(3)	4e	0.4446(5)	-0.4300(7)	0.2114(1)	0.060(3)	0.080(3)	0.053(2)	0.012(3)	-0.001(2)	0.000(2)
C(4)	4e	0.1632(5)	-0.1992(6)	0.22164(9)	0.068(3)	0.050(2)	0.036(2)	0.005(2)	0.007(2)	0.005(2)
C(5)	4e	-0.0094(5)	-0.1758(7)	0.2021(1)	0.064(3)	0.043(2)	0.048(2)	0.004(2)	0.013(2)	-0.003(2)
C(6)	4e	-0.2086(5)	0.0911(7)	0.1724(1)	0.059(3)	0.055(3)	0.065(2)	0.010(2)	0.002(2)	-0.007(2)
C(7)	4e	-0.1994(5)	0.0485(6)	0.1307(1)	0.044(2)	0.042(2)	0.060(2)	0.006(2)	0.000(2)	-0.002(2)
C(8)	4e	-0.2696(5)	-0.1478(6)	0.1137(1)	0.056(3)	0.049(2)	0.067(3)	-0.002(2)	0.004(2)	-0.003(2)

Table 3. (Continued)

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
C(9)	4e	−0.2632(6)	−0.1812(7)	0.0750(1)	0.077(3)	0.057(3)	0.076(3)	−0.004(3)	−0.002(2)	−0.018(2)
C(10)	4e	−0.1801(6)	−0.0185(9)	0.0531(1)	0.074(3)	0.089(4)	0.060(3)	0.018(3)	0.005(2)	−0.001(3)
C(11)	4e	−0.1063(6)	0.1768(8)	0.0700(1)	0.067(3)	0.077(3)	0.082(3)	−0.004(3)	0.008(3)	0.020(3)
C(12)	4e	−0.1161(5)	0.2119(7)	0.1086(1)	0.068(3)	0.052(3)	0.073(3)	−0.007(2)	−0.007(2)	0.002(2)
C(13)	4e	0.3519(4)	−0.6028(6)	0.1466(1)	0.045(2)	0.041(2)	0.053(2)	0.002(2)	0.012(2)	0.008(2)
C(14)	4e	0.3310(4)	−0.5542(6)	0.10537(9)	0.044(2)	0.037(2)	0.046(2)	0.000(2)	0.009(2)	−0.001(2)
C(15)	4e	0.3922(5)	−0.7213(6)	0.0802(1)	0.059(3)	0.048(2)	0.056(2)	0.008(2)	0.006(2)	−0.004(2)
C(16)	4e	0.3747(5)	−0.6833(8)	0.0415(1)	0.071(3)	0.062(3)	0.062(3)	0.003(2)	0.009(2)	−0.019(2)
C(17)	4e	0.2949(5)	−0.4849(8)	0.0275(1)	0.076(3)	0.078(3)	0.046(2)	−0.002(3)	0.007(2)	0.001(2)
C(18)	4e	0.2315(5)	−0.3207(7)	0.0520(1)	0.075(3)	0.059(3)	0.059(3)	0.007(2)	0.002(2)	0.009(2)
C(19)	4e	0.2521(5)	−0.3534(6)	0.0909(1)	0.061(3)	0.044(2)	0.051(2)	0.006(2)	0.008(2)	−0.001(2)

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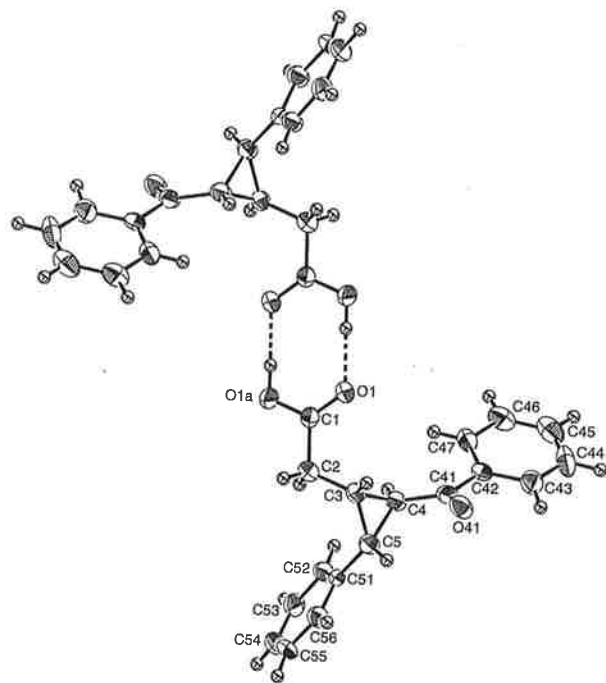
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Crystal structure of 2-(2-benzoyl-3-phenylcyclopropyl)acetic acid, $C_{18}H_{16}O_3$

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$C_{18}H_{16}O_3$, monoclinic, $P12_1/n1$ (No. 14), $a = 5.878(3)$ Å, $b = 13.995(8)$ Å, $c = 17.355(3)$ Å, $\beta = 92.70(3)^\circ$, $V = 1426.1$ Å³, $Z = 4$, $R(F) = 0.060$, $R_w(F) = 0.064$.

Table 1. Parameters used for the X-ray data collection

Crystal:	colorless needle, size 0.15 x 0.18 x 0.52 mm
Wavelength:	Mo $K\alpha$ radiation (0.7107 Å)
μ :	0.88 cm ⁻¹
Diffractometer:	Rigaku AFC6R
Scan mode:	$\omega/2\theta$
$T_{\text{measurement}}$:	220 K
$2\theta_{\text{max}}$:	50°
$N(hkl)_{\text{unique}}$:	1501
Criterion for I_σ :	$I_\sigma > 3 \sigma(I_\sigma)$
$N(\text{param})_{\text{refined}}$:	254
Program:	TEXSAN

Table 2. Final atomic coordinates and displacement parameters (in Å²)

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso}
H(1)	4e	-0.134(9)	0.500(5)	0.052(3)	0.10(2)
H(2a)	4e	0.210(8)	0.418(4)	0.199(3)	0.07(2)
H(2b)	4e	0.070(6)	0.326(3)	0.170(2)	0.03(1)
H(3)	4e	0.544(6)	0.360(3)	0.138(2)	0.03(1)
H(4)	4e	0.247(6)	0.201(2)	0.088(2)	0.018(9)
H(5)	4e	0.622(6)	0.225(2)	0.208(2)	0.019(9)
H(43)	4e	0.859(6)	0.082(3)	-0.011(2)	0.04(1)
H(44)	4e	0.790(7)	-0.003(3)	-0.131(2)	0.05(1)
H(45)	4e	0.424(7)	0.004(3)	-0.197(3)	0.06(2)
H(46)	4e	0.142(6)	0.104(3)	-0.149(2)	0.04(1)
H(47)	4e	0.211(6)	0.185(3)	-0.036(2)	0.03(1)
H(52)	4e	0.037(6)	0.146(3)	0.194(2)	0.04(1)
H(53)	4e	-0.174(7)	0.088(3)	0.291(2)	0.04(1)
H(54)	4e	-0.019(7)	0.098(3)	0.413(2)	0.05(1)
H(55)	4e	0.346(6)	0.166(3)	0.440(2)	0.03(1)
H(56)	4e	0.556(6)	0.224(3)	0.343(2)	0.03(1)

Source of material: A mixture of 353 mg (1.56 mmol) 3,6-diphenyl-3,6-dihydro-1,2-dioxine (see refs. 1 and 2) was allowed to react with 705 mg (1.72 mmol) of benzyl 2-(triphenyl-λ⁵-phosphanylidene)acetate (see ref. 3) in anhydrous benzene (10 ml) under a nitrogen gas atmosphere at ambient temperature for three days. Removal of the volatiles and silica gel chromatography afforded the cyclopropyl ester which was hydrolysed with excess base. Removal of the volatiles and extraction with dichloromethane (4 x 50 ml) afforded the title compound (see ref. 4). Recrystallisation from an ether solution of the compound; mp 429 K – 431 K.

The compound crystallises as a single diastereoisomer in a racemic crystal: about the cyclopropyl ring, the H(4) atom is in trans position with respect to the H(3) and H(5) atoms. Molecules associate as centrosymmetric dimers such that O(1a)–H...O(1)' is 1.76(6) Å, O(1a)...O(1)' is 2.669(4) Å and the O(1a)–H...O(1)' angle is 177(2)°.

Table 3. Final atomic coordinates and displacement parameters (in Å²)

Atom	Site	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
O(1)	4e	0.2071(5)	0.4268(2)	0.0275(2)	0.045(2)	0.053(2)	0.033(2)	0.015(2)	0.013(1)	0.006(2)
O(1a)	4e	-0.0938(5)	0.4648(2)	0.0949(2)	0.041(2)	0.049(2)	0.043(2)	0.018(2)	0.017(1)	0.014(2)
O(41)	4e	0.7893(5)	0.2171(2)	0.0766(2)	0.030(2)	0.071(2)	0.033(2)	0.001(2)	0.003(1)	0.002(2)
C(1)	4e	0.1049(7)	0.4224(3)	0.0871(2)	0.039(3)	0.031(2)	0.034(3)	0.007(2)	0.010(2)	0.002(2)

Table 3. (Continued)

Atom	Site	x	y	z	U ₁₁	U ₂₂	U ₃₃	U ₁₂	U ₁₃	U ₂₃
C(2)	4e	0.1903(8)	0.3702(4)	0.1579(3)	0.043(3)	0.042(3)	0.032(3)	0.005(2)	0.008(2)	0.005(2)
C(3)	4e	0.4097(7)	0.3179(3)	0.1480(2)	0.030(2)	0.035(3)	0.031(2)	-0.001(2)	0.007(2)	0.004(2)
C(4)	4e	0.4018(7)	0.2216(3)	0.1077(2)	0.028(2)	0.043(3)	0.028(2)	0.000(2)	0.001(2)	0.004(2)
C(5)	4e	0.4638(7)	0.2290(3)	0.1945(2)	0.028(2)	0.044(3)	0.029(2)	0.002(2)	0.001(2)	0.002(2)
C(41)	4e	0.5910(7)	0.1948(3)	0.0581(2)	0.032(2)	0.043(3)	0.029(2)	0.003(2)	0.003(2)	0.009(2)
C(42)	4e	0.5381(7)	0.1413(3)	-0.0146(2)	0.040(3)	0.034(3)	0.028(2)	-0.001(2)	0.009(2)	0.010(2)
C(43)	4e	0.7096(8)	0.0857(3)	-0.0442(3)	0.047(3)	0.041(3)	0.046(3)	0.000(2)	0.014(2)	0.005(2)
C(44)	4e	0.668(1)	0.0357(4)	-0.1125(3)	0.067(4)	0.045(3)	0.057(4)	-0.002(3)	0.034(3)	-0.014(3)
C(45)	4e	0.461(1)	0.0415(4)	-0.1511(3)	0.080(4)	0.049(3)	0.040(3)	-0.017(3)	0.016(3)	-0.004(3)
C(46)	4e	0.2912(9)	0.0976(4)	-0.1232(3)	0.057(3)	0.064(4)	0.035(3)	-0.005	-0.001(3)	0.001(3)
C(47)	4e	0.3295(8)	0.1463(3)	-0.0541(3)	0.043(3)	0.052(3)	0.031(3)	0.005(3)	0.007(2)	-0.002(2)
C(51)	4e	0.3193(6)	0.1904(3)	0.2553(2)	0.028(2)	0.030(3)	0.025(2)	0.009(2)	0.005(2)	0.005(2)
C(52)	4e	0.1053(7)	0.1502(3)	0.2419(3)	0.030(2)	0.045(3)	0.029(3)	0.002(2)	0.001(2)	0.004(2)
C(53)	4e	-0.0168(8)	0.1145(3)	0.3020(3)	0.034(3)	0.044(3)	0.044(3)	0.002(2)	0.010(2)	0.003(2)
C(54)	4e	0.0676(8)	0.1229(4)	0.3769(3)	0.047(3)	0.050(3)	0.038(3)	0.003(2)	0.018(2)	0.010(2)
C(55)	4e	0.2775(8)	0.1637(4)	0.3912(3)	0.053(3)	0.058(3)	0.019(2)	0.012(3)	0.005(2)	0.004(2)
C(56)	4e	0.4039(7)	0.1964(3)	0.3315(2)	0.036(3)	0.045(3)	0.032(3)	0.001(2)	0.001(2)	0.000(2)

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